Summary and Response to Public Comment for the Proposed CIRM MES Regulations

Postings 5/22/09, 10/30/09 and 11/18/09
Prepared 1/14/109

Standards Regs 100070 and 100090 Posting 5/22/09 Comments

#	Section	Summary of Public Comment(s) 5/22/09	Response to Public Comment	Ref.
1	100070(d)	**[Note comments for section 100070 are summarized for informational purposes and because they overlap with related sections.]** CIRM received three substantially similar comments: This proposed revision was discussed at a recent meeting of the UCI HSCROC. Concern was expressed about the use of the term "notification" for review of projects using induced pluripotent stem cells. The concern is simply that our committee has no formal procedure at other comparable committees. We are concerned that investigatory may misinterpret this section to indicate that notification procedures are in place and available when they are not. The term "notification" for review of projects using induced pluripotent stem cells is unclear and inconsistent with formal practice of similar committees in the regulatory field such as IRB and IACUC. As also noted by Dr. Golub in his submitted comments, investigators may misinterpret this section to indicate that notification procedures are in place and available when they are not. Therefore, I suggest a modification of the proposed rule to indicate that existing review procedures such as full committee, expedited or administrative review may be used by the responsible institutional oversight committee, depending on its procedures and the content of the proposed	The language proposed for adoption now includes an option for a "statement from the designated institutional official" or notification of the SCRO committee. The inclusion of the statement as an option would alleviate the concern raised by the commenter while simultaneously allowing institutions that have established SCRO notification procedures to continue to utilize this procedure (note Stanford comments endorses notification approach). CIRM requires grantees to document SCRO notification prior to awarding grantee funding. CIRM intends to require the statement from the designated institutional official to also be submitted prior to funding. CIRM believes either option serves the policy goal of providing assurance that acceptable research materials are being utilized by CIRM-funded researchers. *(d) CIRM-funded purely 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 (section 100040(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.*	SG_7/5/09 SP_7_6_09 MK_7_6_09 AH_6_30_09

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		study. In addition, one commenter indicated support for the notification approach in the May 22, 2009 draft.		
2	100090	CIRM should authorize use of embryos created for reproductive purposes regardless of the date of the creation of such embryos. … The guiding principle should remain the prevention of undue influence of gamete or embryo donors to participate in research. That being said, embryos made for clinical IVF purposes with the assistance of paid donors is a separate clinical issue from payment for research oocytes. The clinical IVF donor is not being paid for research but rather to assist in clinical reproduction. Stanford also generally concurs with the amendment to Section 100090(a)(1), which allows for the use of embryos created from gametes from which the donors were paid solely for reproductive purposes (lVF). However, we would encourage CIRM not to limit the use of these embryos to those created on or before August 13,2008. Because the third party's private agreement to serve as a gamete donor for fertility purposes is entirely separate from any decision to donate extra embryos for research we do not believe that there is any payment for a research donation, and hence no reason to assign an arbitrary date to this section.	The language proposed for adoption no longer includes a cutoff date for the use of embryos made for clinical IVF purposes. CIRM concurs that the clinical IVF donor is not being paid for research, and therefore there are no restrictions on the use of such embryos. Section 10080(a)(2)(B) was revised to remove the general prohibition on the use of clinical IVF embryos. *For embryos originally created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose "valuable consideration" does not include payments to original gamete donors in excess of "permissible expenses." Original gamete donors may receive reimbursement for permissible expenses as defined in California Code of Regulations, title 17, section 100020, subdivision (h),*	SP_7_6_09 AH_6_30_09

Standards Regs 100070 and 100090 Posting 10/30/09 Comments

#	Section	Summary of Public Comment(s) 10/30/09	Response to Public Comment	Ref.
1	100090(a)(1)	The proposed revised section (a)(1) opens the door to payment for oocytes by allowing women to be paid for their eggs for embryos that are used in research. Proposition 71 prohibits payment to anyone who provides biological materials for research, and this revision should not be adopted. Note the section numbers cited in comments appear to be inconsistent with the revisions posted for comment. CIRM believes the commenter may have been referencing the May 22, 2009 posting. The language governing use of embryos created using in vitro fertilization for reproductive was subsequently incorporated into section 100080(a)(2)(b) and posted on November 27, 2009. CIRM's response to public comment is intended to be responsive to the commenter regardless of section.	Proposition 71 charges the ICOC with establishing standards "prohibit compensation to research donors, while permitting reimbursement of expenses." (Health and Safety Code 125290.35(b)(3). The commenter's concern is effectively addressed by the proposed the creation of a new section, 100090(b), which states: *CIRM funds may not be used to provide valuable consideration to donors of gametes, embryos, somatic cells or tissue…* Section 100090(b) was deliberately incorporated in this round of regulatory revisions to make clear CIRM funds may not be used to compensate research donors. In addition to the prohibition in section 100090(b), the proposed amendments incorporate a distinction between the procurement of biological materials for (1) clinical/medical treatment and (2) research purposes that is well established in existing state regulations and national guidelines. (1) Health and Safety Code 125325 applies to persons or entities *seeking **oocyte** donation associated with the delivery of fertility treatment that includes assisted **oocyte** production and a financial payment or compensation of any kind*. (2) Health and Safety Code 125335 applies to the procurement of *oocytes for research or the development of medical therapies*. Section 1000080(a)(2)(B) incorporates the distinction to provide a narrow exemption to *embryos originally created using in vitro fertilization for reproductive purposes and were no longer needed for this purpose.*	PCARR_11_16_09

#	Section	Summary of Public Comment(s) 10/30/09	Response to Public Comment	Ref.
			CIRM incorporated language consistent with state regulations and identical to *The National Academies' Guidelines for Human Embryonic Stem Cell Research* (NAS Guidelines). In doing so, CIRM believes it is clear to the regulated community that only materials for which compensation was received by the donors in association with the delivery of fertility treatment may be utilized in CIRM-funded research. The proposed amendment addresses an inconsistency inadvertently incorporated into CIRM policy. This policy is inconsistent with policies in other states, the NAS Guidelines and the National Institutes of Health. Specifically, no other jurisdiction imposes a restriction on the use of embryos created for reproductive purposes that would otherwise be discarded. This specific amendment removes this restriction and serves to align CIRM policy with California, other state and national standards.	
2	100090(a)(1)	Recent research reveals the ability to ascertain the identity of gamete donors through a new "method that allows detection of a single person's SNP profile in method that allows the detection of a single person's SNP profile in a mixture of 1,000 or more individual DNA samples." In light of this information presented in the recent paper *NIH Background Fact Sheet on GWAS Policy Update,* the term "cannot be identified" is unclear and vague. This section should not be adopted without significant clarification as to the steps that must be taken to come to the conclusion that the sperm donor cannot be identified.	The proposed amendment is consistent with established state and federal policy for research involving biological specimens. The proposed regulation was widely disseminated to effected parties and none indicated this provision was unclear or vague. Established Federal policy equates identifiably with the presence of direct identifiers or codes associated with the specific sample: *OHRP considers private information or specimens to be individually identifiable as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.* http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.pdf It is understood within the research community that the term "cannot be identified" refers to the absence of direct identifiers or a coding system that would enable identification of the donor.	PCARR_11_16_09

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			The commenter is discussing a theoretical circumstance that is outside the common regulatory use of this term. Further, the possibility of identifying a sperm donor from an embryo is implausible for the following reasons. • When sperm and egg combine a unique genome is created due to the mixing of genetic material. • With regard to the specific technique referenced in the comment, it is important to recognize that in order to ascertain the identity of a gamete donor from a sperm, one would need to already be in possession of a genetic profile from the donor and know the identity of said donor. *To find a specific profile within a set, the inquirer would first need to already have a highly-dense genomic profile (currently at least 10,000 SNPs) from an individual. http://grants.nih.gov/grants/gwas/background_fact_sheet_20080828.pdf* The proposed amendment is consistent with well-established state and national policy governing the utilization of biological specimens in research.	
3	100090	We suggest that §100090 be revised as follows: Add section (a)(3) The physician attending to any donor and the principal investigator shall not be the same person unless exceptional circumstances exist and an IRB has approved an exemption from this requirement. (a)(4) The physician performing oocyte retrieval shall not have a personal or financial interest in the outcome of the research.	Section 100090(a)(3) was incorporated in response to this comment. *(3) For research involving the use of embryos originally created using in vitro fertilization for reproductive purposes, the physician performing oocyte retrieval may not be the CIRM-funded principal investigator unless the SCRO has approved an exemption from this requirement.* CIRM references SCRO approval for an exemption because embryos are not human subjects, and, therefore, the IRB may not have jurisdiction over the review and approval process for such research. The CIRM regulations require a SCRO committee to review and approve all CIRM-funded research involving human embryos.	PCARR_11_16_09

Standards Regs 100070 and 100090 Posting 11/18/09 Comments

#	Section	Summary of Public Comment(s) 11/16/09	Response to Public Comment	Ref.
1	100090(a)(1)	We appreciate the proposed addition of section (a)(3) as a first step in addressing the inherent conflicts of interest between researchers and fertility clinics and physicians. However, we remain concerned that this provision still does not prohibit the fertility clinic or physician from having a personal or financial interest in the research. Failure to address this conflict also fails to ensure that research interests do not compromise the fertility interests and health and welfare of potential embryo donors. We suggest that §100090 be revised further as follows to reflect the CIRM Grants Administration Policy (GAP) for Academic and Non-Profit Institutions which is incorporated by reference into the GAP for For-Profit Institutions: (a)(3) For research involving the use of embryos originally created using in vitro fertilization for reproductive purposes, the physician performing oocyte retrieval or the attending physician responsible for infertility treatment may not be the CIRM-funded Principal Investigator (as defined in tile 17, California Code of Regulations, section 100500) or a Key Personnel on a CIRM-funded grant (as defined in the CIRM Grants Administration Policy (GAP) for Academic and Non-Profit Institutions and the CIRM	CIRM has received comments #1 5/22/09 indicating there are procedures and polices in place to ensure the fertility interests of potential embryo donors. Despite these protections, section 100090(a)(3) was incorporated in response to PCARR_11_16_09 comment #3. *(3) For research involving the use of embryos originally created using in vitro fertilization for reproductive purposes, the physician performing oocyte retrieval may not be the CIRM-funded principal investigator unless the SCRO has approved an exemption from this requirement.* The 12/3/09 suggestion expands the scope of the 11/16/09 comment. Expanding the scope of this requirement, as proposed, is burdensome and relies on undefined terms. For example, a "personal" conflict of interest. CIRM received testimony and comments (5/22/09 posting) documenting the separation between (1) clinical/medical treatment and (2) research. There are also numerous protections to ensure the fertility interests of potential embryo donors. • The CIRM regulations include extensive informed consent requirements for potential donors (Section 100100(b)) • The state penal code, 367g, makes it unlawful for anyone to knowingly use sperm, ova, or embryos in assisted reproduction technology, for any purpose other than that indicated by the sperm, ova, or embryos provider's signature on a written consent form.	PCARR_12_3_09

#	Section	Summary of Public Comment(s) 11/16/09	Response to Public Comment	Ref.
		Grants Administration Policy (GAP) for For-Profit Institutions) unless the SCRO has documented extraordinary circumstances and approved an exemption from this requirement. (a)(4) The physician performing oocyte retrieval shall not have a personal or financial interest in the outcome of the research.		
2	100090	We appreciate CIRM's attention to issues of conflicts of interest. However, we remain concerned that the proposed changes are inadequate. From the point of view of maintaining and promoting women's health (which is the only justifiable position that a woman's physician should take), permitting any association between an IVF physician and a researcher seeking embryos created with donor eggs presents inherent conflicts of interest. Asking a woman to siphon off some of her embryos for use elsewhere undermines the integrity of the infertility treatment. Even more problematic is the health and welfare of egg donors who are an unprotected source of raw materials. Reports of egg yields between 12 and 15 often are referenced as typical but we have spoken to young women from whom two and three times that many eggs have been taken. In light of the absence of oversight of the egg harvesting process, there should be no conflict of interest that would encourage, even unconsciously, an unsafe administration	CIRM believes in the interest of promoting women's health and safety there may be a compelling need for a CIRM principal investigator (PI) to have clinical interaction with an egg donor. The proposed amendment is modeled after CIRM's existing policy governing donation of oocytes exclusively for CIRM-funded research. Section 100095(d) states: *The physician attending to any donor and the principal investigator shall not be the same person unless exceptional circumstances exist and an IRB has approved an exemption from this requirement.* The general prohibition with an exemption provision was incorporated to balance conflict of interest concerns with women's health and safety. For example, a CIRM principal investigator may bring clinical expertise in assisted reproduction. Based on testimony provided during policy deliberations, CIRM believes it would be highly improbable for the CIRM principal investigator to be the same person as the individual who performed oocyte retrieval for reproductive purposes. Oocyte retrieval for reproductive purposes is very different than the circumstance addressed by section 100095(d) where oocytes are retrieved and then directed immediately to research. In a reproductive context, oocytes are retrieved and embryos are then created for clinical use. Typically, at least two years pass before individuals may decide to end clinical fertility treatment. If a couple or	AHB_12_3_09

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		of that process. The conflicts of interest are intractable. They undermine the fiduciary responsibilities of medical practitioners. The only ethically responsible position to take is to ensure that there is a firewall between physician and researcher. It is not too late for CIRM to do the right thing, reconsider, and pull back from an unethical path that violates the spirit of the law passed by the citizens of California.	individual has excess embryos after treatment, research donation represents one option among many for disposition. In other words, there is no way to know in advance if individual would donate to research. Further, as emphasized during policy deliberations, an extensive informed consent process is required for donation to CIRM funded research. Despite the improbability of the CIRM principal investigator being the same person and the multiple levels of protection already incorporated into CIRM regulations, section 100090(a)(3) was incorporated. *(3) For research involving the use of embryos originally created using in vitro fertilization for reproductive purposes, the physician performing oocyte retrieval may not be the CIRM-funded principal investigator unless the SCRO has approved an exemption from this requirement* CIRM disagrees with the assertion that the conflicts are "intractable." To the extent any conflict may exist, the revisions remedy this conflict by requiring a clear separation between clinical are research activities.	

#	Section	Summary of Public Comment(s) 11/27/09	Response to Public Comment	Ref.
1	100090(a)(2)(B)	The proposed revised section (a)(2)(B) opens the door to payment for oocytes by allowing women to be paid for their eggs when the embryos they create are used in research. This proposed change in the regulation creates a loophole that could easily swallow the rule – creating a legal maneuver around Proposition 71 which prohibits payment to anyone who provides biological materials for research. Health & Safety Code § 125290.35(b)(3) directs the ICOC to "establish standards prohibiting compensation to research donors or participants, while permitting reimbursement of expenses." "Research donor means a human who donates biological material for research purposes after full disclosure and consent." Health & Safety Code § 125292.10(t). The proposed revision seeks to evade this provision of the law and should be rejected.	As the commenter has emphasized, there is a distinction in established California and national policy between biological materials obtained with the intent of (1) delivering a clinical/medical treatment and (2) performing research. Consider the following examples: (1) Health and Safety Code 125325 applies to persons or entities *seeking **oocyte** donation associated with the delivery of fertility treatment that includes assisted **oocyte** production and a financial payment or compensation of any kind*. (2) Health and Safety Code 125335 applies to the procurement of *oocytes for research or the development of medical therapies*. The National Institutes of Health, the National Academies of Sciences California, and numerous states make this distinction with the deliberate intent of providing individuals with the option of donating embryos originally created for reproductive purposes. These same jurisdictions allow donation of reproductive embryos (regardless of the payment status of gametes) while simultaneously prohibiting payment for oocytes obtained with the exclusive intent of performing research. The commenter's "loophole" concern is effectively addressed by the proposed the creation of a new section, 100090(b), which states: *CIRM funds may not be use to provide valuable consideration to donors of gametes, embryos, somatic cells or tissue…* Section 100090(b) was deliberately incorporated in this round of regulatory revisions to make clear CIRM funds may not be used to compensate research donors.	PCARR_1_11_10