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

Prepared for ICOC Consideration 08/02/06

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
1	100010	The intent of the regulations is described as pursuing research "that protect[s] patient safety, patient rights, and patient privacy." The use of the term "patient" is confusing since many of the "subjects" would not be patients, especially in oocyte, sperm, and somatic cell donors. It seems unfortunate that the preamble focuses solely on patients. Perhaps, patients, donors, and other subjects would be a viable alternative?	This comment refers to language in a working draft that was circulated prior to OAL notice. This language was removed from the 3/17/06 OAL filing since it is non-regulatory.	2-47 WC012
	100020	**Definitions**		
	100020 (a)	No direct comments		
	100020 (b)	No direct comments		
2	100020 (c)	"covered stem cell line" as part of working out conditions, stem cell lines may not always be sustainable in culture. Some cultures may die prematurely or could be lines driven to the last step: terminal differentiation, such as a culture of insulin-producing beta islet cells derived from hESCs. Those cultures will grow temporarily, then die.	This comment is addressed in revised section 100070(c) *CIRM-funded research with the aim to derive or create a covered stem cell line*. Research intended to derive line, regardless of their latent development, requires SCRO committee review.	2-52 WC013 WC017-6
3		"covered stem cell line" not all stem cells are capable of differentiating into multiple lineages. Germ stem cells are unipotent, and can only make oocytes and spermatocytes (but can self-renew). There may be as-yet undiscovered unipotent stem cells.	Revised definition focuses on "pluripotent-potential" and intent of derivation. See below.	2-53 WC013
4		**CONCERN** Proposed definition of what would be required for review: *"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"* This narrows the definition somewhat less than all adult stem	One of many comments concerning potential ambiguity in the definition of "covered stem cell line." The term "multiple cell lineages" was identified as broad and ambiguous. The intent of the definition is to capture cell lines of "pluripotent-potential" not all stem cells. Definition revised to read: *"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*	2-56 WC015 WC016-1 WC018-1 WC018-3 WC018-4

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		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. There is no need to extend ESCRO review to include all adult stem cell research, because this is already required under the California Health and Safety Code to be reviewed by the IRB. Also, many of the ethical concerns are being driven not by the potential uses of the cells, but by their origin in human blastocysts. Stem cell scientists on our committee felt that the field is not yet able to provide clear scientific criteria to predict pluripotency of adult derived cell lines. The entire committee was uncomfortable with the current vague wording of this section which might well include typical adult bone marrow derived stem cells. We suggest limiting ESCRO involvement to stem cells that have been clearly shown to have pluripotent capacity (or where the experiments are designed to cause pluripotency) or when the IRB asks for SCRO consultation. **PROPOSAL** The definition should revert to an earlier version so that we don't have to duplicate a kind of review that is already adequately covered by the IRB. However, whether or not this is the case, the wording of this section should be more explicit about what is actually to be covered.	*differentiation into mesoderm, ectoderm, and endoderm.* The commenter is correct in stating that the primary moral and ethical concerns are over the use of oocytes and blastocysts and there is uncertainty over scientific criteria to predict pluripotency. Recognizing these points the regulations do not hinge on this definition; rather the use of oocytes and blastocysts trigger review of research independent of the definition of "covered stem cell line". In addition, the regulations also focus on research "intended" to derive pluripotent cell lines as a trigger for additional review.	
5	100020 (d)	The term "funded research" is used throughout the proposed regulations to define which research must comply with the proposed regulations. Any and all research which is funded fully or partially with public funds must be required to comply with the regulations, including research performed by a CIRM-funded trainee and research conducted in a CIRM-funded facility. Therefore, for clarification, we propose adding the following language: Funded research: add/revise . . . *all activities performed by*	The Grants Administration Policy addresses the disposition of materials, equipment and the responsibilities of CIRM-funded trainees. It also outlines policies on what constitute acceptable direct- and indirect-costs. These requirements will be described in a separate regulatory filing and should not be duplicated by including such language in this filing.	2-78 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		CIRM-funded trainees, all training activities supported by CIRM funds, research or training conducted in facilities funded in whole or in part by CIRM, research utilizing equipment purchased with CIRM funds shall be considered funded research."		
6	100020(e)	This definition should be expanded to include any persons who undergo a procedure for the research that entails significant risk, including providing oocytes. [2] In addition, add (e)(3) original providers of subsequently anonymized tissue/oocytes/sperm and other human genetic material are still to be considered human subjects.	The existing definition is identical to the Code of Federal Regulations Title 45 Public Welfare DHHS Part 46 Protection Of Human Subjects (the Common Rule). The comment reflects a false premise. This definition is unambiguous; any person involved in a physical procedure, regardless of the level of risk, is considered a *human subject*. IRB administrators were queried on this issue and none could conceive of conditions where an oocyte donor for research would not be considered a human subject. It is clearly recognized in regulation and practice that i*ntervention* includes both physical procedures by which data are gathered (for example, venipuncture) and interactions with the subject or the subject's environment. Existing regulations and practice are clear that anonymized tissues are not considered human subjects. Research that involves neither interactions nor interventions with living individuals or obtaining identifiable private information is not considered human subjects research. Research using already derived and established human cell lines, from which the identity of the donor(s) cannot readily be ascertained by the investigator, are not considered human subject research and are not governed by the HHS or FDA human subject protection regulations appearing at 45 CFR Part 46 and 21 CFR Parts 50 and 56. IRB review is not required for such research. The proposed definition would create a direct conflict with existing state regulations including but not limited to Health and Safety Code Section 24170-24179.5 Protection of Human Subjects in Medical	2-79 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
			Experimentation Act.	
	(f)	No direct comments		
	(g)	No direct comments		
7	(h)	We recommend against including "actual lost wages" as a permissible expense. The justification of including lost wages as a permissible expense is to give all women the opportunity to provide eggs. While this may appear to treat all women equally, in reality it recreates great disparities between women and in fact disrespects them by assigning them a value based on their earning capacity, when in fact they are each providing exactly the same service. The economic advantages of middle class women are recreated in the laboratory when lost wages are reimbursed. First, low income women are least likely to be given permission by their employers to take time off from work, more likely to have jobs that are paid hourly, or to provide services in the informal economy such as domestic work or piece work. Therefore, they will probably provide eggs on their own time, using a day off, and will not be able to document any lost wages at all and the lost wages reimbursement will not benefit them. Middle class women, on the other hand, are more likely to have jobs that would allow them to take personal time, and they will be paid either by their employers or by the researchers. The result is anything but equality. A more equitable system is to be clear that providing eggs for research is an act of altruism and treat all women the same. We propose that "actual lost wages" be deleted as a permissible expense.	This comment is directed at a major policy recommendation of the Standards Working Group; the basis for which is extensively documented in the SWG record. This policy is entirely consistent with well developed international reimbursement policies, notably Canada and the United Kingdom, governing egg donation. IRBs are sensitive to issues pertaining to the recruitment of human subjects. IRBs are bound by state and federal laws that prevent discriminatory practices in participant selection. *45 CFR §46.111 Criteria for IRB approval of research.* *(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:* *(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.* The assertion of harm is highly speculative and contrary to established practices in clinical research. Indeed, as suggested by comments from membership organizations representing women, low-income women who have actual lost wages would suffer further	2-80 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
			financial disadvantage if they were not permitted to recover their lost wages.	
8		I support compensating women and other tissue donors for their contribution to this vital area of research. We support the decision to include "actual lost wages" as permissible expenses. In fact, we would request too include some sort of compensation for the 50-60 hours of medical care (blood tests, hormone shots, ultrasounds and the actual oocyte extraction procedure) endured over an approximately one month period, but understand that is not possible given the language of Proposition 71. Especially given that there is no compensation or honorarium for this selfless act, it is only fair to women to have them fully reimbursed whatever expenses they incur when they subject themselves to this process. We understand that some view reimbursement of lost wages as discriminatory as some women make more than others. However, the lack of any reimbursement for lost wages could make it impossible for lower and middle income women to be able to participate, where an upper income woman could absorb loss of income more easily. In fact, if the upper income woman is a salaried professional, she might not even	Reimbursement policy is defined by CA H&S code 125290.35(b)(3) *The ICOC shall establish "standards prohibiting compensation to research donors or participants, while permitting reimbursement of expenses."* Compensation may only be provided for expenses no additional compensation is allowed.	2-64 2-77 WC019-1 WC021 WC029

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		lose income for the hour here and there when she needs to come in for a blood test, if she is not paid hourly by her employer. If she does not lose wages, she will not be paid for her time by the research project, as the regulations limit reimbursement to "actual lost wages1[2]". As CIRM needs fairness and diversity in research, the language on lost wages should be retained.		
	(i)	No direct comments		
9	100020(j)	The definition of somatic cell nuclear transfer should encompass those procedures in which the donor nucleus is introduced prior to oocyte enucleation, (e.g. Munsie et al. Current Biology 10:989, 2000). Arguably the coverage should also extend to reprogramming to pluripotentiality by cell fusion or other means.	The definition was revised to read: *"Somatic Cell Nuclear Transfer" ("SCNT") means the transfer of a somatic cell nucleus into an oocyte.*	2-71 WC025
	(k)			
	S 100030	**Activities Not Eligible for CIRM Funding**		
	(a)	No direct comments		
	(b)	No direct comments		
	(c)	No direct comments		
10	(d)	It would help if embryo was a defined term. This would clarify whether to allow (c) a human NSC transplant into a primate in utero "late embryo" at 7 weeks, for example (not exactly sure where monkey embryogenesis ends). For (d) or (e), identifying whether transplants of stem cells into late stages of human embryogenesis is permitted, up to 8 weeks.	SWG considered at 5/3/06 meeting, added clarifying language as prohibiting the transfer of a genetically modified human embryos to a uterus. SWG recognized additional issues may arise with regard to transplantation, but policies relating to such issue should be discussed in the context of future policy recommendations. In addition, the SWG anticipates this issue may be discussed by the NAS Committee recommending guidelines for embryonic stem cell research. Future CIRM policies may be informed by the NAS deliberations.	2-54 WC013
11		The embryonic period is generally understood in man to extend to 8 weeks of development. It is conceivable that introduction of stem cells (broadly defined) before this time point into the postimplantation, postgastrulation embryo might be desirable, for example to correct genetic or other congenital	The regulations state that such activities are not eligible for CIRM funding. The SWG concurred at it 5/3/06 meeting that therapeutic interventions might be desirable at some time in the future. The SWG thought it was important to balance this theoretical potential with social concerns over the application of this technology. The	2-72 WC025

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		disorders. Also, it is possible that introduction of cells into animal embryos postimplantation, post gastrulation, might be desirable, to determine the developmental potential of the cells. The intent here is to avoid formation of chimeras in which the donor cells contribute extensively to multiple tissues. It is arguable that this is an area better served by a regulatory approach with flexibility rather than proscriptive legislation.	provisions remain, consistent with the NAS Guidelines.	
12		Ultimately, the same technologies that may be developed with CIRM funding can be used for good or for disturbing purposes such as human reproductive cloning, which though illegal in California and explicitly prohibited by Proposition 71 has not been legislatively prohibited in most U.S. states or at the federal level. The CIRM regulations appropriately draw boundaries that cannot be crossed using CIRM funds. In order to achieve that goal, we propose that the language in §100030 be strengthened as follows: [1] The opening sentence should read, "CIRM funds shall not be used to directly or indirectly promote the following activities:" [2] An additional type of research that has been prohibited in more than 30 countries and that should not be eligible for CIRM funding is inheritable genetic modification of human beings. Therefore we propose adding the following as not eligible for funding: (f) The transfer of a genetically modified nucleus or stem cell, or an artificial chromosome, into a human oocyte or embryo. (g) The genetic alteration of a human embryo.	[1] The Grants Administration Policy addresses the disposition of materials, equipment and the responsibilities of CIRM-funded trainees. It also outlines policies on what constitute acceptable direct- and indirect-expenditures. [2] The SWG introduced sub-section (d): *The transfer to a uterus of a genetically modified human embryo.* The focus on transfer to the uterus captures the range of concerns associated with creating offspring who are genetically modified in ways that would be transmitted to future generations.	2-81 WC022
	(e)	No direct comments		
	(f)	No direct comments	New section developed in response to comment #12 (f-g)	
	S 100040	**Institutional Assurance of Compliance**		
13	100040(a)	(a) Should be modified to read "The Office of President, Chancellor, or equivalent chief executive office shall be responsible for..." the written report. The regulations need to spell out the required content of the written assurance in order to ensure proper accountability. The following should be	*Section revised to read: Each institution 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;*	2-75 WC024 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		added: (a) 1. The written assurance must include a report of the data collected as required in the record keeping provisions of Section 1000120. (2) The written assurance must be delivered annually. (3.) The written assurance must be sent to the Secretary of Health, the Assembly and Senate Health Committees and the CIRM. (4) The written assurance will be made available to the public. An exception for public release may be made for data about individually identifiable patients or research subjects and for proprietary information. (5) The institution must contract with an outside service to audit the institution's compliance with these standards annually. The audits will be released publicly. (6) Failure to comply with these requirements shall result in any or all of the remedies in Section 100050.	A new section 100070(h) has been introduced requiring annual renewal of SCRO committee renewals. Substantial reporting requirements exist in the CIRM Grants Administration policy (GAP) as they relate to the required reviews and notification. For example, The GAP requires reporting of SCRO and IRB review or notification requirements. Assurances must be sent to CIRM and these documents become part of the public record. The remedies described in section 100050 apply to all CIRM regulations. No standards currently exist for how an outside audit contract would be structured.	
14	(b)	(1) was modified to require that a Chancellor or chief executive officer, etc., designate the Institutional Official (IO) responsible for oversight of CIRM sponsored research. The modification was an important change to the regulations. Nevertheless, as currently revised, a Chancellor, etc., could name an IO that is a dept chair, division chief, faculty without chair status, therefore, an individual that does not have the authority to (a) garner the respect of the entire institution, (b) promulgate and enforce institution wide policies, and (c) create an institutional ethos consistent with the importance and sensitivity of hESC research and the CIRM requirements. RECOMMENDATION: The regulation should explicitly state that the IO should be a person who has the legal authority to act and speak for the institution and who can effectively ensure that the institution will fulfill its research oversight responsibilities by promulgating and upholding appropriate research policies, procedures, and oversight.	A person with "plenary" authority would be a person with full, complete or absolute authority. The existing language serves the intent sated in this comment. It is important to recognize that CIRM may fund non-academic institutions where position titles may vary. The intent here is to identify the performance standard for oversight where the person certifying compliance has complete and absolute institutional authority.	3-113 WC036

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
	(c)	No direct comments		
	(d)	No direct comments		
	S 100050	**Compliance**		
	(a-h)	No direct comments		
	S 100060	**SCRO Committee Membership and Function**		
15	100060(a) General	The intent of the "public" member does not appear to have been met. The current revised 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 the intent of the NAS guidelines is to include a non-scientist public member and this could be achieved by stating as much.	SWG considered at 5/3/06 meeting, modified language to read *one non-scientist member of the public*.	2-48 WC012
16		[1] Just as the NIH conducts oversight of IRBs, reviews their protocols, and rules on the appropriateness of their conduct, California needs a similar state authority to oversee and review SCROs. Operation of SCROs at the local level without oversight invites inconsistent standards and procedures and lacks any fail-safe mechanism to detect misconduct or omissions or failures to comply with law and regulations. Therefore, CIRM should work with state officials to establish such a SCRO oversight body that is independent of the CIRM. [2] A position in the SCRO at any institution that intends to perform egg extraction or SCNT should be reserved for an expert in women's health. [3] No member of the SCRO should be supervised by a recipient of a CIRM grant. No member of a SCRO should have a personal or financial interest in any aspect of the research endeavor that is likely to come before the committee for approval. If such research does come before the committee, the member must be recused. Recusal should also apply to patient advocates when decisions are made about the disease constituency the patient advocate represents. No member of a SCRO at a for-profit company should have any	[1] The Department of Health and Human Service's Office of Human Research Protection approves IRB assurance, but does not conduct direct oversight of IRBs. The ability to establish an oversight body independent of the CIRM is outside the institute's constitutional authority. CIRM will consider procedures and policies to review the conduct of SCRO committees. Such procedures may include but not be limited to review of SCRO committee approvals and reporting on policies regarding participant reimbursement. In addition, the CIRM Grants Administration Policy requires documentation and reporting of compliance with reviews pursuant to these regulations. [2] The inclusion of a member with expertise in "assisted reproduction" is intended to provide expertise in a specific and most relevant aspect of women's health. Section 100070 (a) *CIRM-funded research involving the procurement or use of human oocytes may not commence without SCRO committee review and approval in writing. For such SCRO committee review and approval, a member of the committee with expertise in assisted reproduction shall be present.*	2-82 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		personal or financial interest in the company beyond basic remuneration for their time served on the SCRO.	[3] Additional language intended to address conflict of interest added. see response to comment #17.	
17		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? 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).	Language considered by SWG and revised to be consistent with 45 CFR 46.107(e). *(e) No SCRO committee may have a member participate in the SCRO committee's initial or continuing review of any project in which the member has a professional or financial stake, except to provide information to the IRB.*	2-49 WC012
18		1. Permissible Expenses. The May 9 revisions to Section 100060(a) added language stating that members of the SCRO committee may be reimbursed for "permissible expenses, as defined in Title 17, California Code of Regulations, section 100020, subdivision (h)." This language does not appear to accomplish your apparent intent of allowing institutions to pay or reimburse SCRO committee members for their committee service, since the cited definition of "permissible expenses" includes only costs incurred as "a result of donation or participation in research activities." SCRO committee members neither donate materials to nor participate in the research they are reviewing. The current language therefore appears to preclude them from receiving payment or reimbursement from the institution. This problem could be addressed by eliminating the restriction on institutions remunerating SCRO committee members, as follows: § 100060. SCRO Committee Membership and Function. (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	We concur with the comment that the use of undefined terms or terms that are not consistent with general practice introduces uncertainty. Further in this section Federal Conformity is desirable for the purpose of developing the least burdensome alternative. Therefore, this section has been revised to mirror current federal regulations relating to conflicts of interest and Institutional Review Boards (45 CFR 46.107). The term "conflicting interest" is applied. Because institutions are familiar with implementing conflict of interest rules using this term, its use in the CIRM regulations would facilitate institutional efforts to comply with this section. Also see; 5/5/2004 HHS Guidance: **Final Guidance Document** **Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection** The issue of payment to non-scientist members was discussed extensively within the Standards Working Group. The proposed policy received public comment and support and was approved by the SWG. Given the firm policy basis for this provision, it should not be modified at this time.	3-103 WC034

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		the public who is not employed by, or appointed to, or remunerated by the relevant research institution. Any member of a SCRO committee member may be reimbursed for permissible expenses, as defined in Title 17, California Code of Regulations, section 100020, subdivision (h). In addition, a SCRO committee shall include at least one patient advocate. . . . . . Such a change would allow institutions to choose to pay public non-scientist SCRO committee members for their committee service and/or to reimburse them for actual expenses incurred in connection with their committee service, which would avoid disadvantaging the public members (since the regulations do allow payments and reimbursements to SCRO committee members affiliated with the institution). Alternatively, language could be added specifying that institutions may reimburse SCRO committee members for expenses associated with their SCRO committee service.		
19		**Conflict of Interest.** The May 9 revisions also modified Section 100060(a) to prohibit a SCRO committee member from participating in "the SCRO committee's initial or continuing review of any project in which the member has a professional or financial stake except to provide information to the IRB." This replaced the previous requirement that "No SCRO committee member may have a financial conflict of interest in the research under review." <u>The term "professional or financial stake" is undefined, and it is unclear whether/how this differs from a conflict of interest</u>. While we understand and support the goal of examining significant non-financial as well as financial interests in determining whether there is a conflict that should preclude participation, the use of the undefined term "professional or financial stake" could lead to confusion, as it leaves out the concept of a conflicting interest. In addition, it is unclear why the current language refers to providing information to the IRB, rather than to the SCRO committee. This problem could be addressed by using language that	We concur with the comment that the use of undefined terms or terms that are not consistent with general practice introduces uncertainty. The OAL requires under the APA that standards be clear and consistent. Federal Conformity is desirable for the purpose of developing the least burdensome alternative and ensuring clarity and consistency. Therefore, this section has been revised to mirror current federal regulations relating to conflicts of interest and Institutional Review Boards (45 CFR 46.107). The term "conflicting interest" is applied.	3-104 WC034

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		mirrors current federal regulations relating to conflicts of interest and Institutional Review Boards (45 CFR 46.107). The federal regulations use the term "conflicting interest." Because institutions are familiar with implementing conflict of interest rules using this term, its use in the CIRM regulations would facilitate institutional efforts to comply with this section. The following modification to Section May 24, 2006 Page 4 Comments on CIRM draft Medical and Ethical Standards Regulations 100060 would mirror the regulations that apply to IRB members, and address the concern about the use of an undefined term: § 100060. SCRO Committee Membership and Function. (a) . . . . .No SCRO committee may have a member participate in the SCRO committee's initial or continuing review of any project in which the member has a professional or financial stake conflicting interest, except to provide information to the SCRO committee IRB.		
20		The changes to this section have brought some welcome clarity to the issues of the nonscientific, nonaffiliated member. However, additional explication would do a great deal towards ensuring the appropriate participation and respect for the nonscientific, nonaffiliated member. Similar to the HHS IRB requirements for full participation of this important committee member, the regulations should require the attendance of such a member at a convened ESCRO/SCRO meeting in order for the committee to vote on research activities. 45 CFR 46.108 provides a model with minor modification: RECOMMENDATION: "Except when an expedited review procedure is used, the ESCRO/SCRO shall review proposed research at convened meetings at which a majority of the members of the ESCRO/SCRO are present, including at least one nonscientific, nonaffiliated member." a. Quorum: The regulation does not indicate whether a quorum of the members must be present in order to vote on proposed research. The technical modification outlined in #2	The proposed regulations seek to balance the need for exact requirements with California legislative findings and declarations under the Administrative Procedure Act which states: *The imposition of prescriptive standards upon private persons and entities through regulations where the establishment of performance standards could reasonably be expected to produce the same result has placed an unnecessary burden on California citizens and discouraged innovation, research, and development of improved means of achieving desirable social goals.*[CA Government Code Section 11340(b)] In the area of stem cell research oversight committee composition and operation, CIRM identified a number of innovative approaches to achieving the fundamental goal of ethical and scientific review of stem cell research. Given this area of organizational oversight in new and in a formative stage of development, the standards avoid prescriptive details for SCRO operation in areas such a quorum	3-114 WC036

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		above and this quorum provision would ensure *CIRM Proposed Medical and Ethical Standards, CA Code of Regulations* page 2 discussion and votes require the participation of a majority of members, including the nonscientific public membership. RECOMMENDATION: The above recommendation for #2 would address this concern. If you disagree with #2, I recommend the following: "In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting." b. Payment of ESCRO/SCRO Members: Though the Working Group modified the ESCRO/SCRO payment restrictions for participation on the committee, the currently revised regulation references Section 100020(h): remuneration for donation or participation in research activities. Such a reference is not applicable to membership on the ESCO/SCRO. The decision whether to pay ESCRO/SCRO members and the appropriate amount of payment should be at the discretion of the Institution and not directed by the CIRM nor should the State prohibit paying for the important contribution and service of SCRO/ESCRO members. 45 CFR 46.107(d) provides appropriate model language: "Each [ESCRO/SCRO] shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution." The phrase "…not otherwise affiliated…" will ensure that the "public" nonscientist may be paid for services rendered for the ESCRO/SCRO, as determined by local institutional policy, while also defining the concept of "public" member. RECOMMENDATION: Remove all references to payment unless it is to clarify that an Institution may pay SCRO/ESCRO committee members for their participation on the committee. Revise 100060(a) as follows: "A SCRO committee shall include at least one nonscientist	issues. The issue of payment to non-scientist members we discussed extensively within the Standards Working Group. The proposed policy received public comment and support and was approved by the SWG. Given the firm policy basis for this provision, it should not be modified at this time.	

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		member of the public who is not employed by, appointed to, or remunerated by the relevant institution *otherwise affiliated with the relevant research institution and who is not part of the immediate family of a person who is affiliated with the institution*. Any member of a SCRO committee member may be reimbursed for permissible expenses, as defined…." (1) The same section indicates, "…in which the member has a professional or financial stake, except to provide information to the *IRB* [emphasis added]." It appears the Working Group has confused the ESCRO/SCRO with the IRB at the end of the sentence. The referenced committee should be the "ESCRO/SCRO". (2) Conflict of Interest (COI) [100060(a)]: The COI rules should be sufficiently broad to include many forms of COI and not just "financial or professional conflicts." 45 CFR 46.107(e) provides model language that is simple, appropriately broad, and flexible enough to address multiple *CIRM Proposed Medical and Ethical Standards, CA Code of Regulations* page 3 forms of COI while mirroring regulations that are familiar and implemented by institutions for other committees: RECOMMENDATION: "No SCRO/ESCRO may have a member participate in the SCRO/ESCRO's initial or continuing review of any project in which the member has a conflicting interest, except to provide information to the SCRO/ESCRO."		
	(c)	No direct comments		
	(d)	No direct comments		
	(e)	No direct comments		
	S 100070	**SCRO Committee Review and Notification**		
21	General	Is it really necessary to require ESCRO review of research on tissue stem cells, if they are not pluripotent? Review of research protocols involving donation or therapeutic use of tissue stem cells is carried out by IRBs. ESCRO could be notified of such activity with cross reference to IRB approval. Further downstream experimentation in vitro with such cells	The applicable SCRO committee review requirements of Section 100070 apply to (a) use of human oocytes, (b) use of human embryos, and (c) efforts to derive covered stem cell line. The definition of "covered stem cell line" was revised to emphasizes culture-derived pluripotent cell lines. Human cancer cells would not fit this definition.	2-71 WC025 WC018-2

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		could be also subject to notification to an ESCRO, as could animal experiments; where a protocol involving introduction of tissue stem cells into experimental animals might raise exceptional ethical issues, the ESCRO could opt to review the protocol. IRB and ESCRO review should not be redundant. The definition here should also explicitly exempt established or immortalized human cell lines other than ES, EG or SCNT/reprogrammed cell lines. Many established cell lines derived from human cancers, and used by thousands of laboratories daily, might be captured by this definition. The proposed definition has the potential to require at least minimal review by an ESCRO/SCRO Committee of in vitro research with human adult stem cells. However, such research is, by definition, already subject to IRB review under California's Health and Safety Code, and either donation for research or any human research uses of such cells requires IRB review under Federal as well as California regulations. In the case that an IRB believes it does not have the necessary expertise to review a particular protocol, it has always had the option to request ad hoc expertise as needed. In the case of this area of research, consultation with the ESCRO/SCRO Committee would be one such option. However, it would not be a good use of resources to have two different committees conduct the same review. We recommend instead to focus on the principle that such review should occur, rather than to specify which committee should be responsible for that review. This would give each institution the flexibility to develop its own effective mechanisms for review.	Animal experiments are subject to review if they involve covered stem cell lines or implantation of neural progenitor cells to the brain of animals. The SCRO review process is intended to complement existing review processes with specific expertise related to issues that emerge in stem cell research. This point is elaborated upon in the NAS report. There is sufficient flexibility in the regulations to prevent duplicative reviews by committees.	
22		Human subject protections should apply to all women who provide eggs for research. We are very concerned that §100080 and 100090 of the proposed regulations create two classes of egg providers – those who are guaranteed access to medical care and other subject protections, and those who aren't. Some research funded by CIRM will include the	Section 100080(e) applies to all stem cell lines used in CIRM-funded research. This section requires core human subjects protections (voluntary informed consent and IRB review) be in place for all covered cell lines used in CIRM-funded research (see definition of "human subject" and response to comment #6). These protections include but are not limited to all women who provide	2-84 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		derivation of embryonic stem cell lines, and the women who provide the eggs for those lines will be covered by §100090 and have access to medical care and other subject protections. Other CIRM funded research, however, will use embryonic stem cell lines derived via SCNT or the creation of IVF embryos with other funding, and the women who provide those eggs will not be afforded those protections. Many ICOC members and CIRM officials made public statements about how CIRM's proposed regulations safeguard women's health, however by allowing CIRM-funded researchers to use eggs (and the stem cell lines derived from them) provided under circumstances that do not meet other CIRM criteria, the regulations create a huge loophole that may significantly undermine women's health. We propose that §100090 be folded into §100080 and that all CIRM-funded research be required to meet the standards of §100090.	eggs for research. The requirements of 100090 and revised 100095 were deliberately recommended as additional requirements for oocyte donation and informed consent in CIRM-funded research. The SWG developed these requirements after extensive deliberation and public input. The SWG unambiguously recommended that such exact and detailed requirements only apply to oocyte donors in CIRM-funded research. This recommendation was base on the judgment that applying the requirements of sections 100090 and 100095 to all research materials used in CIRM-funded research would constitute imposing regulations on stem cell lines derived without CIRM funding, which is outside the authority of CIRM under Proposition 71. Further, such requirements would have the practical effect of restricting materials sharing which would slow the pace of research thus compromising CIRMs major mandate of developing disease therapies. CIRM has no authority to regulate or mandate clinical IVF practice. Regulations concerning the donating oocytes for research that is not funded by CIRM need to be promulgated by the California legislature, which has authority over such research.	
23	100070(a)	All ESCRO committees should be charged with investigating alternatives to egg donation before approving applications to conduct human embryonic stem cell research using fresh human eggs from donation. The following alternatives should be considered in all such cases: a) is there a compelling reason not to do this research using already derived embryonic cell lines? Acceptable reasons might include contamination of existing lines, shortage of lines from some populations, need for training in derivation itself, or need to perfect derivation techniques using a bio-engineered matrix rather than mouse or other mammalian feeder cells. b) is there a way to achieve this goal using adult stem cells?	(a) Research involving existing cell lines is eligible for CIRM funding. An acceptable scientific justification is required for the derivation of new stem cell lines. The SCRO is charged with considering the need for derivation of new cell lines as part of its review and approval process. *100070 (a) CIRM-funded research involving the procurement or use of human oocytes may not commence without SCRO committee review and approval in writing. For such SCRO committee review and approval, the member of the committee with expertise in assisted reproduction shall be present. … At a minimum, the SCRO committee shall require the investigator to:* *(1) Provide an acceptable scientific rationale for the need to use*	2-66 WC019-3

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		Part of this should include a consideration of gender balance: could human sperm progenitor cells be used, for example, for stem cell line derivation and differentiation? Have as many protocols using sperm progenitor cell extraction as egg extraction been approved by this institution? c) could ovarian tissue and in vitro maturation of oocytes be used instead of fresh oocyte harvesting?	*oocytes including a justification for the number needed. If SCNT is proposed a justification for SCNT shall be provided.* (b) All human stem cells are available for achieving the goal. This recognition led to an expansion of the regulation beyond embryonic stem cells. Regulations concerning use of cord blood, fetal tissue and other human tissue have been promulgated in recognition of the value of adult cells. (c) yes, the regulations make explicit reference to human tissue and this is why the informed consent provisions apply to a*ll CIRM-funded human subjects research*.	
24		Membership requirement. The May 9 revisions to sections 100070(a) and (b) require that during SCRO committee review of specified categories of research "the member of the committee with expertise in assisted reproduction shall be present." If there is to be such a requirement, it should be more clearly stated to refer to "a member" rather than "the member" with expertise in assisted reproduction. This reflects the fact that members may have more than one area of expertise (and would avoid implying that SCRO committees must allot one membership "slot" for an assisted reproduction expert, another for a developmental biologist etc.). This is a minor change, but may avoid future confusion.	Section revised to reflect comment.	3-105 WC034
25	(a)(1)	Under (a)(1), if oocytes or embryos are used, the researcher should not only justify the number to be used, but also add the following: Document the planned method of obtaining the oocytes or embryos. If SCNT is used, document what steps will be taken to prevent track the use and disposition of the clonal embryos and prevent their misuse.	Documentation regarding the method for obtaining oocytes would be required for IRB approval pursuant to 45 CFR §46.111. Such information would also be available to the SCRO committee. 45 CFR §46.111 Criteria for IRB approval of research. *(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:* *(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for*	2-83 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
			diagnostic or treatment purposes. The tracking of materials is addressed in Section 100120(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.*	
	(a)(2)	No direct comments		
	(a)(3)	No direct comments		
26	(b)	The requirement for the presence of an expert in assisted reproduction is unduly restrictive for all such research and may negatively impact the ability to approve such research in a timely manner. An individual with expertise in assisted reproduction should not be required and is unnecessary for all research proposing to use stored embryos for laboratory or animal research that meets the CIRM restrictions under Section 100030.	The requirement for a member with expertise in assisted reproduction to be present is in response to a comment intended to protect oocyte donors, and is therefore appropriate in 100070(a) but not this sub-section. The requirement for an expert in assisted reproduction was removed from 100070(b).	3-115 WC036
	(b)(1)	No direct comments		
	(b)(2)	No direct comments		
	(b)(3)	No direct comments		
27	100070(c)	Policies on gamete donation should be extended to include donors of testicular tissue, since recent results indicate that the adult testis is a potential source of pluripotent stem cells (e.g. Guan et al. Nature 440: 1199, 2006) and at least one company in this State is actively conducting research with human tissue in this field.	SWG considered at 5/3/06 meeting, approved modified language: *CIRM-funded research with the aim to derive or create a covered stem cell line may not commence without SCRO committee review and approval in writing.* This language would extend policies to all research intended to derive covered stem cell lines regardless of source. Section 100080(e) Acceptable Research Materials, applies to all donors of *gametes, embryos, somatic cells or <u>human tissue</u>*. Again extending protections to all potential sources of research material.	2-70 WC025
	(c)(1)	No direct comments		
	(c)(2)	No direct comments		
	(c)(3)	No direct comments		

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
	(c)(4)	No direct comments		
	(c)(5)	No direct comments		
28	100070(d)	The Standards Working Group has indicated during past public meetings a fundamental goal was to ensure that CA rules were consistent with national standards under the NAS guidelines. Section 100070(d) is inconsistent with the NAS guidelines for review of purely *in vitro* research. The NAS guidelines require (see: NAS: Chapter 6, 1.2(a)) that the ESCRO or equivalent body receive documentation of: (1) the provenance of the cell lines, (2) appropriate informed consent in their derivation, (3) evidence of compliance with any review by an IRB, IACUC, etc. **RECOMMENDATION:** The CIRM regulations should be consistent with NAS guidelines in order to ensure that CIRM funded institutions may share cells in the future with entities outside of California. To this end, the regulation at 100070(d) should require that the ESCRO/SCRO receive and approve documentation of: (a) the provenance of the cell lines, (b) appropriate informed consent in their derivation, and (c) evidence of compliance with any review by an IRB, IACUC, etc.	The CIRM MES meet or exceed the recommendations put forward in the NAS Guidelines. By definition "acceptably derived" section 100080(e) requires informed consent, and the additional requirements of this section would not interfere with the transfer of CIRM funded lines to institutions in compliance with the NAS guidelines.	3-115 WC036
	(d)(1)	No direct comments		
	(d)(2)	No direct comments		
	(e)	No direct comments		
	(e)(1)	No direct comments		
	(e)(2)	No direct comments		
	(e)(3)	No direct comments		
	(e)(4)	No direct comments		
	(f)	No direct comments		
	(f)(1)	No direct comments		
	(f)(2)	No direct comments		
	(f)(3)	No direct comments		
	(f)(4)	No direct comments		
29	(g)	The regulations should clearly indicate whether PIs may	Language considered by SWG and revised to read:	2-51

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		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. We suggest 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."	*Investigators are entitled to reconsideration of a SCRO committee decision. Requests must be made in writing and include a summary of the basis for the reconsideration. Investigators are entitled to be present in order to provide information and responses during the reconsideration.*	WC012
30		The May 9 revisions added language to section 100070(g) that allows investigators to appeal a SCRO committee decision. My understanding is that the revised language was derived from current federal regulations describing the appeal process to be used by IRBs (45 CFR 46.109(d)). However, the language as currently incorporated into the CIRM standards is not entirely consistent with federal regulations; greater consistency would clarify the intent and scope of this section, and would ease implementation by allowing institutions to use the existing procedures currently used for appeals of IRB decisions. The following modification is suggested to better mirror the federal regulations: (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. Investigators are entitled to reconsideration of a SCRO committee decision. Requests must be made in writing and include a summary of the basis for the reconsideration. Investigators are entitled to be present in	Section revised to read: *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.*	3-105 WC034

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		order to provide information and responses during the reconsideration.		
31		**Appeal of ESCRO/SCRO decisions:** This section attempts to address an important point related to the integrity of the ESCRO/SCRO authority as an oversight body. However, refining the regulation would clarify the intent, provide important flexibility in determining the level of review of such appeals, and provide familiar ground for the implementation of the regulation: **RECOMMENDATION:** Replace the current revised regulation with the following: "Covered research that has been approved by an ESCRO/SCRO may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an ESCRO/SCRO. An ESCRO/SCRO shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure such approval of the research activity. If the ESCRO/SCRO 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."	Section revised to read: *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.*	3-115 WC0036
32	(h)	This Section references for the first time "expedited review" but does not explain the requirements for such a review. In order to ensure consistency across all institutions for expedited review, it would be appropriate to define the regulatory term and outline a process for the review. Additionally, an individual ESCRO/SCRO member should not be allowed to disapprove a renewal application absent deliberation and vote of the convened committee. 45 CFR 46.110 provides a sound model for the renewal review process while ensuring that disapproval is only determined by the convened committee: **RECOMMENDATION:** "Under an expedited review	There is nothing in the recommended regulations that would prevent an intuition from establishing the recommended procedures. The proposed regulations seek to balance the need for exact requirements with California legislative findings and declarations under the Administrative Procedure Act which states: *The imposition of prescriptive standards upon private persons and entities through regulations where the establishment of performance standards could reasonably be expected to produce the same result has placed an unnecessary burden on California citizens and discouraged innovation, research, and development of improved*	3-115 WC0036

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		procedure for renewal of research, the review may be carried out by the ESCRO/SCRO chairperson or by one or more experienced reviewers designated by the chairperson from among members of the committee. In reviewing the research, the reviewers may exercise all of the authorities of the ESCRO/SCRO except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the nonexpedited procedure set forth in *[insert appropriate section]*."	*means of achieving desirable social goals.*[CA Government Code Section 11340(b)] In the area of stem cell research oversight committee composition and operation, CIRM identified a number of innovative approaches to achieving the fundamental goal of ethical and scientific review of stem cell research. Given the relative recent development of ESCRO/SCRO committees, we prefer to allow intuitions to develop appropriate procedures and policies. Should it be determined that further regulation is necessary, the SWG may recommend additional procedures for review.	
	S 100080	**Acceptable Research Materials**		
33	General	Given the particular level of risk, and the absence of any direct benefit to anyone, all egg providers should be afforded the protection of human subjects. We propose [creating a new section]: (e)(6) All women who provide oocytes for research are human subjects and afforded all rights and protections required under state and federal law and regulation.	Sections 100090, 100095 and 100100 apply to all CIRM-funded research involving oocytes. These provisions include but are not limited to all rights and protections under state and federal law for human subjects. Section 100100 reads: *(a) All CIRM-funded human subjects research shall be performed in accordance with Title 45 Code of Federal Regulations, Part 46 (Protection of Human Subjects), revised June 23, 2005, and California Health and Safety Code section 24173.* By definition, egg donation for research constitutes human subjects research. Any person involved in a physical procedure, regardless of the level of risk, is considered a *human subject*. It is clearly recognized in regulation and practice that i*ntervention* includes both physical procedures by which data are gathered (for example, venipuncture) and interactions with the subject or the subject's environment. See response to comments #22 and #6.	2-86 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
34	100080(a)(b)(c)	Approved cell lines might be extended to include those derived by a licensee of the Australian National Health and Medical Research Council, whose regulations are in line with those of other bodies cited here.	CIRM was not able to confirm Australian equivalency; such lines are eligible if they comply with 100080(e).	2-73 WC025
	100080(d)	No direct comments		
	(e)(1)	No direct comments		
	(e)(2)	No direct comments		
35	100080(e)(3)	It is only advisable to withhold payment to egg donors if no one at any point from procurement to therapeutic application stands to benefit financially from CIRM funding; in other words, if all players are restricted to direct-cost-compensation-only altruism. As this is not the case, it sets up a prima facie economic disenfranchisement, placing a burden of altruism on egg or tissue donors alone. I thus support compensating women and other tissue donors for their contribution to this vital area of research.	The SWG is constrained by Proposition 71 which prohibits payments to donors or for cells. *125290.35. Medical and Scientific Accountability Standards* *(a) Medical Standards* *.. The **ICOC**, its working committees, and its grantees shall be governed solely by the provisions of this act in the establishment of standards, the award of grants, and the conduct of grants awarded pursuant to this act.* *(b) The **ICOC** shall establish standards as follows:* *(3) Prohibition on Compensation* *Standards prohibiting compensation to research donors or participants, while permitting reimbursement of expenses.* *(5) Limitations on Payments for Cells* *Standards limiting payments for the purchase of stem cells or stem cell lines to reasonable payment for the removal, processing, disposal, preservation, quality control, storage, transplantation, or implantation or legal transaction or other administrative costs associated with these medical procedures and specifically including any required payments for medical or scientific technologies, products, or processes for royalties, patent, or licensing fees or other costs for intellectual property.* Changes to compensation policy would require legislative action or a initiative.	2-64 WC019-1

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
			Section 100080(e)(3) also prohibits financial gain form the procurement of gametes, embryos, somatic cells, or human tissue.	
36		It is important not to pay anyone what would amount to an undue inducement to undertake medical risk in tissue donation. To make sure that only an appropriate amount is paid in compensation, the following criteria should be met: a) tissue, especially embryos and gametes, should not be valued differently according to eugenic criteria. There should be a flat rate to compensate the work involved in each donation, regardless of donor characteristics, match potential, or earning power of the donor. b) The numbers of eggs retrieved per donation also should not affect the lump sum paid for the effort and contribution of the donation. This would be wrong on two grounds: it would compensate the wrong thing (eggs instead of effort), and it would encourage hyperstimulation protocols that increased yield, potentially substituting yield for the health of the donor. c) payment should be calculated according to civil service pay scales and on the basis of the hours and effort involved, in consultation with area fertility experts and CA government human services.	(a) The compensation criteria in the MES regulations are limited to out of pocket expenses. There may be differential reimbursements based on "earning power," but this decision is made by an IRB, and not prescribed by the regulations. This issue received extensive discussion by the SWG; at its 01/30/06 meeting. (b) Reimbursement policy is related to time spent and expenses incurred not the number of eggs retrieved. (c) IRBs may establish limits on compensation, but compensation should not exceed out of pocket expenses. The CIRM GAP will require funded researchers to document their reimbursement policies.	2-65 WC019-2
37		The phrase "except for donors as provided in subdivision (e)(2) of this regulation" should be deleted as it suggests that there is an exception that does not exist. The reference back to (e)(2) is confusing because (e)(2) allows reimbursement of expenses, not valuable consideration.	Revised to read: *A person may not knowingly, for valuable consideration, purchase or sell gametes, embryos, somatic cells, or human tissue for research purposes pursuant to this chapter. This provision does not prohibit reimbursement for permissible expenditures as approved by a SCRO committee or IRB, or permissible expenses as determined by an IRB.*	2-85 WC022
	(e)(4)	No direct comments		
	(e)(5)	No direct comments		
	S 100090	**Additional Requirements for CIRM-Funded Derivation**		
		No direct comments		
	100095 (100090)	**Additional Requirements for CIRM-Funded Research Involving Oocytes**		
38	General	The following ways to mitigate potential harm to egg donors	SWG considered at 5/3/06 meeting, modified language to read:	2-67

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		should be implemented: a) short term risks to donors should be minimized by: i) only permitting SART registered clinics, and qualified fertility physicians to handle stimulation protocols and egg extraction for fresh egg donation ii) best practice monitoring for, and where necessary treatment of, ovarian hyperstimulation syndrome and other potential side effects during and immediately after treatment, provided at no cost to the donor iii) state wide data collection to monitor side effects of egg donation and compare outcomes between egg donation for fertility services and for stem cell research b) long term risks to donors should be minimized by: i) minimizing gonadotropin exposure by restricting limiting donation to not more than one or two donations and fine tuning stimulation protocols according to donor response ii) where possible, use ovarian tissue section rather than oocyte harvesting. The development of protocols to biopsy ovarian surfaces for immature oocytes should be funded. iii) ovarian section should be restricted to women already undergoing pelvic surgery, such as tubal ligation or exploratory laparoscopy, or to cadaveric extraction with informed consent according to the prevailing standards for organ donation. There should be a prohibition on the use of abortuses for this purpose. Methods for ovary biopsy by ultrasound aspiration should be explored. iv) Studies to perfect in vitro maturation of human oocytes should be funded. v) data should be collected state wide on the long term effects of egg donation, particularly but not exclusively, the use of gonadotropins. Data on the subsequent health of children born to women who were in their past egg donors should also be monitored. vi) while data is being collected on the possible risk of donation-induced subsequent infertility, this fear should be	*(a) The clinic performing oocyte retrieval is a member of the Society for Assisted Reproductive Technology.* *(c) The CIRM-funded institution shall develop procedures to ensure that an individual who donates oocytes for CIRM-funded research has access to medical care that is required as a direct and proximate result of that donation at no cost to the donor.* (a) and (c) are specific provisions intended to protect oocyte donors and provide from immediate treatment at no cost to donors. CIRM does not have authority to mandate state-wide reporting of donor outcomes from all fertility services or stem cell research. Reporting may be required in the context of CIRM-funded research. This point also applies to monitoring of children born to past egg donors. CIRM anticipates obtaining additional recommendations on this topic from an expert panel convened by the Institute of Medicine. These recommendations will inform future policy deliberations and may serve as the basis for new regulations. Note: The above comment was view as meritorious by the SWG and was forwarded to CDHS Human Stem Cell Research Advisory Committee, which has the authority to make recommendations for non-CIRM funded stem cell research. Oocyte donation is a rapidly evolving area of clinical practice. As a policy matter, the SWG feels it is very important to not prescribe specific practices in such a rapidly developing field. Rather procedures and practices should be based on the best currently available information. The primary responsibility of the Institutional Review Board is to minimize risk through ongoing evaluation of scientific evidence and consideration of best practices. *45 CFR §46.111 Criteria for IRB approval of research.*	WC019-4

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		addressed by requiring egg donors to have at least one living child or by requiring that they attest to the desire not to bear children. Informed consent works poorly to cover the risk of infertility, as it is well known that individuals change their minds radically when faced with infertility.	*(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:* *(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.* Thus, the intent of this comment is best achieved through established oversight mechanisms rather than new regulation.	
39		The question of familial and friendship coercion should be addressed. Living tissue donations, especially if uncompensated, risk placing undue burdens on some to donate based on kinship or friendship coercion. This is especially important for egg donation, where the burden falls on women, and where women's kinship and caring roles have long been naturalized and subsumed to the realm of altruism. Women have fought long and hard to have their kinship and caring roles appropriately valued and protected, and well as for the right to take on financially compensated workplace risk. The guidelines as they stand at the moment reverse this effort. The following should be considered: a) Autologous donation should be encouraged. According to the well established bio-ethical principle of justice, benefits and risks should be balanced and the potential to benefit is obviously greatest for patients with conditions that could potentially be treated with stem cell therapies. b) all non-autologous kinds of kinship and friendship donations should be monitored very carefully. This will be critical if the asymmetric altruism of current recommendations is left in place. Women in family and caring roles for patients will be under emotional pressure to donate, and this will be exacerbated by the shortage of other sources of donation. It	(a) Autologous donation (in contrast to donation for research) should be viewed preferentially by the IRB; because the risk benefit equations would shift in the direction of benefit to the human subject. Therefore, it is "encouraged" through existing IRB review procedures. *45 CFR §46.111 Criteria for IRB approval of research.* *(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:* *(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.* (b) SWG should consider whether there should be policies to address non-autologous kinship donations. Again, this issue may be considered in the context of IRB review and approval of research; the IRB is mandated to ensure research subject selection is equitable.	2-68 WC019-5 WC019-6

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		will be especially important to monitor cross generational and the kinds of family power inequities in this regard. Egg donors need to be young and might be particularly vulnerable to these kinds of emotional pressure. The following distinction should be made, and guidelines developed: i) mothers make up one category, and may wish to donate for their children, and should be able to do so with appropriate informed consent that acknowledges their right or need in some medical circumstances to say no or to have a physician say no on their behalf ii) all other kin or friends make up another category, and all potential donors should only make a donation after approval from an IRB or equivalent to establish that they are not being unduly coerced by their relation to a patient. Sample questions might include: do you know anyone who might benefit from your donation? if there were other sources of eggs, or if XXX were not sick, or if YYY had not asked you to consider donating, would you still wish to donate? iii) scientists and physicians should make clear to the best of their knowledge the chances of a donation being used for a therapeutic application, and this information should be communicated to the potential donor as well as to family members if there is any suspicion of emotional pressure to donate.	*45 CFR §46.111 Criteria for IRB approval of research.* *(a) In order to approve research covered by this policy the IRB shall determine that all of the following requirements are satisfied:* *(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.*	
40		This entire section [100090 – 100095] should be moved to division 100080(e).	Section 100080(e) sets standards for acceptable research materials based on national and international principles of research ethics. All stem cell lines used in CIRM-funded research must meet the requirements of this section. The requirements of 100090 – 100100 are additional requirements intended to apply exclusively to human subjects' research and stem cell line derivation performed by CIRM-funded researchers. Apply these additional requirements to all stem cell lines used in CIRM funded research would constitute a de facto imposition of	2-90 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
			CIRM regulations on scientists deriving stem cell lines in other jurisdictions or with other funding sources. The SWG repeatedly expressed a desire not to impose CIRM regulations outside their legal authority. The additional requirements are very specific and exact with regard to procedures and protocols for research. The record reflects the SWG was exceedingly cognizant of the implications of imposing the additional requirements on to all stem cell lines, and, as a matter of policy, recommended that they not be applied.	
	(a)	No direct comments		
41	100095(b)	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. Therefore, this 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.	SWG considered at 5/3/06 meeting, language revised to address comment: *(b) 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.* *(1) A woman providing oocytes for her own reproductive uses may not donate any eggs to research unless she has determined that she does not want or need them to optimize her own chances for reproductive success.* *(2) A woman providing oocytes for donation to another person's reproductive efforts may not donate any of these eggs to research unless (a) the donation is expressly permitted by the recipient who is receiving her oocytes for reproduction and (b) her donation of oocytes for research is done without valuable consideration.*	2-55 WC014
42		**Section 100095 Additional Requirements for CIRM-Funded Research Involving Ooctyes** **<u>Interfering with the doctor-patient relationship:</u>** The intent of the revision of the regulation pertaining to women who provide eggs both for fertility and research purposes was to create clarity, but we are concerned that the new language has not achieved that goal. Instead, the new	CIRM received previous comments indication that meaning of "shall not compromise the optimal reproductive success" needed clarification because the 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 fertility could be impacted by the procedure. This point is developed in the following SWG briefing memo: *SWG_Briefing_Memo_7_19_06.*	3-107 WC035

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		language raises more questions than it answers, and neither researchers nor fertility physicians have been given guidance as to their responsibilities to their patients. Every fertility physician's first responsibility is to her/her patient who is seeking fertility treatment. Therefore, it is unacceptable and a violation of medical ethics, and law, for a physician to compromise the reproductive needs of the patient, either knowingly or negligently. Inserting new intent language into the regulation muddies those obligations, and may even inappropriately shield physicians from liability if their actions do result in not properly providing the fertility treatments that the patient was seeking. Such a result is an impermissible interference in the physician-patient relationship and should be avoided. We propose to strike the word "knowingly" Second, the phrase "the disposition of such oocytes shall not compromise the optimal reproductive success of the woman in fertility treatment" is no moreclear as to what it means to compromise that reproductive success than the original language, it just adds another word - "disposition" - and it is not clear what it changes in this context.	Introduction of the term "knowingly" has no bearing on standards for tort liability, malpractice liability or codes of medical ethics included but not limited to beneficences and the duty of care givers. Further, the language in no way alters any existing obligation of a care-giver; in fact the language specifically intended to support efficacious treatment and care by providing clarity with regards to the intent of this provision. The meaning of disposition of oocytes is specified in the ensuing paragraphs 100095(b)(1) and (b)(2).	
43		**Compensation for egg donors – violation of Proposition 71** The new (b)(2) now creates a loophole that violates the plain language of Proposition 71 which prohibits payment for eggs. This new language allows a clinic to pay a woman for eggs for research by creating a legal fiction and an illusory distinction between eggs provided for fertility and eggs provided for research. Common practice in fertility treatment is to pay women per cycle, not per egg, and in fact, paying women per egg would create perverse incentives as happened in South Korea for women to be given higher doses of hormones than necessary. Suppose a woman provides one cycle of eggs from	The intent of this provision has be clarified with the following language: *(b) For oocytes provided for reproductive uses, either for use by the donor or another woman, the disposition of oocytes shall not knowingly compromise the optimal reproductive success of the woman in infertility treatment.* *(1) Oocytes provided by a woman for her own reproductive uses may not be donated to research unless (a) the woman has determined that she does not want or need them for her own reproductive success, and (b) the donation of oocytes for research*	3-108 WC035

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		which 10 eggs are retrieved. This new regulation says that if a woman undergoes one cycle and provides 10 eggs, the clinic can pay her for 8 and then pretend that she gave 2 for free! This is nothing but a sham to create compensation for eggs for research, which is against the law. This idea has been discussed many times at the Standards Working Group and at the ICOC and has been rejected consistently and should be rejected now. Only women who provide eggs without any compensation can provide eggs for research. We propose the following: <u>(b)(2) A woman providing oocytes for donation for another person's reproductive efforts many not donate any of these eggs to research unless she has received no valuable consideration for her donation of oocytes for either research or reproduction.</u>	*is done without valuable consideration.* *(2) Oocytes provided by another woman for a recipient's reproductive use may not be donated to research unless: (a) the donation is expressly permitted by the oocyte donor; (b) the recipient has determined that she does not want or need them for her own reproductive success, and (c) the donation of oocytes for research is done without valuable consideration.* Under existing law and practice donors routinely enter into agreements with a recipient undergoing IVF treatment. These agreements are developed long before the question of donating eggs to research can be raised. Therefore, the issue of donation of oocytes for research can in no way induce her to enter a paying relationship with a fertility couple nor can it add to any risk she has already taken on. Further, the physician attending to donor cannot be the principal investigator (except under exceptional circumstances). This provision is intended to allow eggs not needed for infertility treatment or eggs that fail to fertilize to be donated to research. These eggs would otherwise be discarded; this provision describes the consent conditions under which the materials may be donated to research. 100095(b)(2) is explicitly intended to protect the rights of the original donor. This decision to donate cannot be made by the clinic and must be done without valuable consideration. The proposed language would add risk by preventing the use of immature or failed-to-fertilize oocytes that could otherwise be donated to research. Allowing the donations of such materials may reduce the need for oocyte donation and thus serve to reduce potential donor risk.	
44		**Compensation for egg donors:** We continue to be concerned that the revised language in	The following actions have been taken in response to the concerns raised in this comment:	4-120-21 & 123-24 WC037 WC039

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		§100095 opens the door to compensation to women who provide eggs for research. This would be a violation of Proposition 71. The plain language of Proposition 71 prohibits compensation to research donors or participants, yet section (b)(2) establishes a loophole that allows research donors or participants to be compensated as long as some of the eggs they are providing are for fertility purposes. The woman providing the eggs in a fertility context must give her consent; she is the donor of record; the informed consent requirements in the regulations apply to her. She is compensated for those eggs. Under Proposition 71, those eggs cannot be used for research. A further concern about allowing women who are paid for eggs to provide some of those eggs for research is that it runs the risk that women will be hyperstimulated to create excess eggs that can then be provided to researchers. At the same time as women's health specialists are urging fertility clinics to reduce the dosages of drugs given to women in order to minimize adverse outcomes, this provision runs against that trend by emphasizing the need for more eggs, not less. This issue of mixed egg donations for compensation was publicly discussed at the January 30, 2006 meeting of the Standards Working Group. On pages 226 to 240 of the online transcript, the clear intent of the Working Groups was that any eggs provided for reproduction purposes for compensation cannot be used for CIRM funded research, even if these eggs failed to fertilize. The current language in question was added by staff in response to comments. Although the revised language was presented at the May 3, 2006 meeting of the Working Group, the issue of mixed egg donations for compensation was not discussed. (See pages 18 to 19 of the online transcript.)	• SWG members were provided with the original comments; • All relevant transcripts addressing the issues "reproductive success" and "failed to fertilize oocytes" were provided to SWG members • Council opinion was sought with regard to constitutionality • Three options for regulatory language were developed and noticed for public comments • See :*SWG_Breifing_Memo_for_7_19_07* • One option; is consistent with the intent of the commenter • The SWG was convened to provide a recommendation to the ICOC or the three options • The SWG met on 7/19/06 and recommended option 3 which is consistent with the intent of the commenter. The ICOC will be consulted on 08/02/06 to provide final resolution.	WC040

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		The ICOC has neither discussed nor approved this proposal. Moreover, when the issue of compensation has been raised in the past, CIRM staff, leadership, and legal counsel have clarified again and again that women cannot be paid for their eggs for research. For example, at one Standards Working Group meeting, one of the members suggested there might be ways to do an end run around the compensation prohibition, and CIRM president Dr. Hall and others stated clearly that is not acceptable. We understand from CIRM staff that the intent in creating this loophole is to make eggs that fail to fertilize available to researchers. However, there should be a separate public discussion by the ICOC on this sensitive issue, and CIRM staff should ask for complete legal and scientific analyses. As this would be a major revision of the proposed regulations, such a provision should not be considered hastily or under the radar. Furthermore, in a conversation with CIRM staff, it seemed unclear which woman would be the egg provider in this mixed context. If Woman A gives some of her eggs to Woman B for the latter's reproductive wishes, and then Woman B provides some of these eggs for research, who is the egg provider? If after the first donation, the eggs are considered the property of Woman B, is she the donor? Would Woman A be afforded the safeguards outlined in the Medical and Ethical Standards? We urge you to remove the words "for research" from 100095(b)(2)(c) to clarify that eggs provided for compensation cannot be used for CIRM funded research. We further urge you to explicitly state that a woman who provides for another woman eggs which are later donated for research is afforded		

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		all of the protections for egg providers in the Medical and Ethical Standards. **Interfering with the doctor-patient relationship:** We strongly support regulations that emphasize that physicians treating women and men for infertility owe their first and only duty to their infertility patients. As we commented previously, however, inserting the word "knowingly" in the mandate not to compromise the reproductive success of fertility patients may have the effect of interfering with that physician's duty. We suggest this section should be reworded to clarify that the physician's duty is only to his/her patient, and as above, additional safeguards and bright lines must be drawn between the fertility clinic and the research.		
45		The recent CIRM draft regulations regarding egg "donation" which seek to legitimize procuring eggs for research from women undergoing IVF is ill-advised. Women undergoing IVF are in a vulnerable position both psychologically and physically. Their health as well as the integrity of the IVF procedure should not be jeopardized by competing concerns unassociated with their desire to have a child. Suggesting regulations that would facilitate acquiring excessive numbers of eggs from women undergoing IVF only serves to underscore that the aims of SCNT advocates are at odds with women's health and well-being. The most ethical position for the ICOC to adopt is a moratorium on egg donation until such time as independent scientific research establishes that it will cause neither short nor long term harm to women. Medical practitioners should not be asked to compromise their responsibilities to protect their patient's health.	Procuring oocytes for research cannot compromise the infertility treatment, see: *SWG_Breifing_Memo_for_7_19_07*. The ICOC does not have the authority to adopt a moratorium on egg donation. The regulations through a series of provisions emphasize and reinforce the obligation of providing for the needs of the patient.	4-122 WC038
46	100095(c)	It is important to ensure that non-IVF oocyte donors not bear	Institutions may re-budget to cover the costs of required medical	2-50

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		the costs of non-negligent research related injuries. The requirement that the Institution assume sole responsibility for the "cost of any medical care required as a direct and proximate result of oocyte donation for research" is very inconsistent with NIH rules under A-21 and FDP that allows for budget reallocation that does not substantially change the scope of the project in order to address subject injury. Alternatively, the Institution could ask to re-budget to help cover the cost of medical care for the non-negligent injury. The re-budgeting would occur in the direct costs. It seems that CIRM should share some of the financial responsibility for the cost of care resulting from non-negligent injury, at least through re-budgeting of the grant.	care.	WC012
47		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.	SWG considered at 5/3/06 meeting, language revised to address comment: *The CIRM-funded institution shall develop procedures to ensure that an individual who donates oocytes for CIRM-funded research has access to medical care that is required as a direct and proximate result of that donation at no cost to the donor.*	2-60 WC017-1
48		We strongly support the requirement that women who provide eggs for research be assured of timely and appropriate medical care for any health outcomes that are a direct result of the oocyte provision procedures. We would like to clarify that the obligation of the institution is to ensure that timely and appropriate medical care is provided and paid for, not merely to provide "payment coverage for medical expenses" as is noted in the draft summary of comments proposed or possible language. Purchasing insurance for women who provide eggs for research may be one mechanism to pay for needed medical care, however the purchase of an insurance policy would not	The revised language is a performance standard where the donor has access to care at no cost; the provision does not specify a particular method of compliance. *The CIRM-funded institution shall develop procedures to ensure that an individual who donates oocytes for CIRM-funded research has access to medical care that is required as a direct and proximate result of that donation at no cost to the donor.*	2-88 WC027

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		be sufficient. Transforming this obligation into an insurance model does not fulfill the objective of the regulation, and leaves women subject to the terms of the insurance product.		
49		Regarding the provision of medical care for any adverse medical outcome, the time frame in which adverse outcomes occur varies from woman to woman, and the word "proximate" is ambiguous and fails to give proper guidance to researchers. The word "direct" is sufficient and more accurate as it clarifies that any adverse outcome that is caused by the egg provision process must be treated by the researchers. The American Society for Reproductive Medicine Ethics Guidelines state that medical care should be provided for any "direct" result of the procedure. (b)(2) We propose to delete the word "proximate".	A "direct and proximate cause" is an unambiguous term recognized in law. The SWG recognized there are short-term, well-characterized complications that may arise from oocyte retrieval. The term "proximate" is used in this sub-section to make clear to researchers they are responsible for required medical care required as a result of complications that result directly and next to in time from oocyte retrieval. The SWG members deliberately recommended this language in recognition that compensation for injuries historically has not been adopted because of difficulties in calculating the long-term actuarial risk and taking into account intervening factors that contribute to or cause adverse events.	2-87 WC022
50		**Assuring medical care** With regard to the provision of medical treatment for adverse outcomes from the egg provision process, we agree with the clarification that medical treatment shall be provided to women at no cost, however, we believe further clarity is required to ensure that the woman is not required to use her own health insurance. As discussed at length in the Standards Working Group, one option may be for the researchers to purchase health insurance for egg providers, and some of these policies are only secondary payors. There may be consequences for women in the long term for using their own insurance such as reaching a life-time benefits cap sooner, exclusions for pre-existing conditions, etc. For women who have insurance, the decision of whether to use that insurance must be left to the woman. <u>Therefore, we propose adding a new sentence at the end of (c): If a donor is medically insured, the donor shall not be required to claim any such medical treatment through her own health</u>	There is no identified vague or ambiguous term in the regulation. The scenario the comment describes would clearly constitute a cost because health insurance is paid for, directly or indirectly, by the donor. The proposed language makes this point explicitly and the section was revised to read. *(c) The CIRM-funded institution shall develop procedures to ensure that an individual who donates oocytes for CIRM-funded research has access to medical care that is required as a direct and proximate result of that donation at no cost to the donor. If a donor is medically insured, the donor shall not be required to claim any treatment costs through her own insurance policy.*	3-109 WC035

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		insurance policy.		
51	(d)	The physician attending the egg provider should not be affiliated with the research. The potential for conflict of interest is too great to be tolerated. The 2000 Federal Guidelines for Research Using Human Pluripotent Stem Cells recognize the potential for conflict and state, "the attending physician responsible for the fertility treatment and the researcher or investigator deriving and/or proposing to utilize human pluripotent stem cells should not have been one and the same person." There should be *no* exceptions to this rule. We propose to delete the phrase, "unless exceptional circumstances exist and an IRB has approved an exemption to this requirement."	The SWG agrees that conflicts of interest should be minimized. However, it concluded there may be circumstances where in the interest of patient safety if the principal investigator possessed unique clinical qualifications, the principal investigator should be able to attend to a donor. This conclusion is consistent with the conclusion of the National Academies of Science which states: *Whenever it is practicable, the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells should not be the same person.* It should be emphasized that an "exceptional circumstances" is the highest standard for an exemption, and IRBs should be extremely reluctant to grant such a wavier unless compelling circumstances exist. For example, a principal investigator might be uniquely experienced in the region for using lower doses of hormonal stimulation in oocyte retrieval. Excluding her from research would be contrary to be best interests of oocyte donors.	2-88 WC022
52		With regard to conflicts of interest, as we noted above, the revised language recognizes that professional conflicts of interest can be just as damaging as financial conflicts. We propose that the same language used in the SCRO committee provisions should also apply here. We propose the following revision: (e) The physician performing oocyte retrieval shall not have a professional or financial interest in any aspect of the research.	The SWG agrees that conflicts of interest should be minimized. However, it concluded there may be circumstances where in the interest of patient safety if the principal investigator possessed unique clinical qualifications, the principal investigator should be able to attend to a donor. This conclusion is consistent with the conclusion of the National Academies of Science which states: *Whenever it is practicable, the attending physician responsible for the infertility treatment and the investigator deriving or proposing to use hES cells should not be the same person.* See Comment #53	3-110 WC035
53		**100095(d):** "The physician attending to any donor and the	The regulations seek to balance concerns over conflicts of interest	3-116

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		principal investigator shall not be the same person unless exceptional circumstances exist and an IRB has approved an exemption from this requirement." CIRM should encourage qualified IVF physician-scientists to participate in CIRM sponsored research as they have much to offer in the deepening of our collective knowledge in this area. The intent of the regulation appears to attempt to address speculative rather than real documented potential harms. Thus, the regulation unduly restricts the ability of IVF physicians to serve as principal investigators of stem cell research that includes subjects who are women interested in oocyte donation for both research ***and*** clinical infertility treatment. An IVF physician/investigator may be the most knowledgeable about the risks of oocyte donation and could play a significant role in the informed consent process. Prohibiting the IVF physician from being principal investigator or obtaining informed consent may unduly restrict the research as well as the information available to potential donor/subjects, ultimately, denying the potential donor/subject a basic ethical tenet of respect through a complete informed consent process. The CIRM regulation will potentially result in nonphysician, nonclinical personnel obtaining informed consent from donors. Such personnel will lack the clinical expertise, experience, and scope of practice to address the ethically and legally mandated aspects of informed consent such as the oocyte donation procedures and the risks of such procedures. The regulation also does not account for the highly personal nature of decisions that are made by individual oocyte donors for clinical IVF and the confidentiality that is often necessary for such a donation. By inserting research personnel into the informed consent process, CIRM ensures that individuals that would not otherwise have a relationship with potential donors unduly intrude on the clinical relationship and confidentiality	with patient safety. The "exceptional circumstance" provision is intended to allow IRB's to grant exceptions in the interest of patient safety.	WC036

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		of the donors.		
54	(e)	We reiterate our concerns that the inherent conflict of interest between research and infertility physician is irreconcilable, and as recommended by the professional organizations, there should be no exception. (d) The physician attending to any donor and the principal investigator or other researcher shall not be the same person.	Proprietary interests are property interests where complete or partial ownership. Consequently, they can be clearly defined. A "Personal interest" is not defined, highly expansive and subject to broad interpretation. Professional interests are also potentially expansive in this context (professional interests are included in 100060). However, in a specialized field, such as reproductive medicine, relations may exist through professional associations or other membership organizations. Ambiguous regulations are undesirable because it is unclear what persons need to do to be in compliance. The fundamental objective in this provision is to remove financial incentives, which would include property interests that might influence the attending physician while balancing issues of patient safety. See comment #53.	2-89 WC022
	S 100100	**Informed Consent Requirements**		
55	General	Lack of clarity regarding applicability to research using existing stem cell lines. It is not always clear in the draft regulations whether provisions are meant to apply retrospectively to existing stem cell lines and to materials donated prior to the enactment of these regulations. It may be helpful to include some clear guidance as to which sections are meant to apply to research using pre-existing cell lines and donated materials. Otherwise, IRBs and ESCROs may have differing interpretations of what is required by the regulations. For example, is Section 100100, setting out specific required informed consent elements, applicable to stem cell lines that were developed prior to the passage of Prop 71? Are researchers precluded from using Prop 71 funds to conduct research using existing stem cell lines if those lines might have been developed from donated materials from donors who were not given the precise elements of information specified by these regulations?	Section 100095 revised to clarify timing. *Where CIRM funds are to be used to derive new human stem cell lines after the effective date of this Chapter, in addition to the requirements of 17 California Code of Regulations section 100080, subdivision (e), the SCRO committee must confirm that donors of gametes, embryos, somatic cells or human tissue have given voluntary and informed consent in accordance with Title17 California Code of Regulations section 100100.*	2-63 WC017-4

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
56		The regulations appear to preclude use of embryos that were collected without the additional informed consent elements listed in section 100100. This poses a problem to researchers who wish to use embryos from our embryo bank (The Stem Cell Resource). I'm sure you know about the Stem Cell Resource, which we started in 2004, before we knew about Prop 71. The embryos donated to the bank, that now number more than 1000, were donated under an informed consent that was written before there was a CIRM. The notable difference is that we did not include a stipulation that embryos could be reclaimed up until the point that they were placed into culture for ES cell derivation. We made the point of no return the arrival of the embryos at the bank, since following that stage, they would only be known by their codes.	Revised language clarifies timing of regulations: *(b) In addition to the requirements of 17 California Code of Regulations Section 100080, the following provisions apply when CIRM funded research involves donation of gametes, embryos, somatic cells or human tissue or derivation of new covered stem cell lines which donation or derivation occurs after the effective date of this Chapter:*	3-98 WC031
57		As currently written, Section 100100 appears to require that the specific disclosures listed in that section be included as elements of informed consent for all CIRM-funded stem cell research, including research using stem cell lines listed on one of the recognized registries or that were developed prior to (or with materials donated prior to) the effective date of the CIRM MES regulations. Such an interpretation is of concern because many lines registered with the NIH and other registries recognized by CIRM (as well as other pre-existing lines) would not meet the standards described in section 100100 and could therefore not be used by CIRM researchers. While Section 100090 does reference Section 100100 in stating that additional informed consent requirements apply where CIRM funds are used to derive future new stem cell lines, Section 100090 does not effectively limit the scope of legal applicability of Section 100100, as was suggested in response to the concerns we raised earlier. The confusion arises from a lack of qualifying language within section 100100. Whereas the scope of section 100090 (as revised) is clearly limited by language reading: "where CIRM funds are to be used to derive new human stem cell lines after the effective date of this	Revised language clarifies timing of regulations: *(b) In addition to the requirements of 17 California Code of Regulations Section 100080, the following provisions apply when CIRM funded research involves donation of gametes, embryos, somatic cells or human tissue or derivation of new covered stem cell lines which donation or derivation occurs after the effective date of this Chapter:*	3-101 WC034

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		Chapter..., " language in section 100100 reads only: "CIRM funds may not be used for research that violates...." Without any qualifying language, the implication is that CIRM funds cannot be used for any research that does not comply with the specific informed consent elements required by Section 100100.		
58	(b)	A technical revision of section 100100, as suggested below (revisions in bold red) would clarify what we understand to be the intended meaning of the section, allowing use of pre-existing cell lines developed from materials donated prior to the enactment of CIRM's regulations, without the need for compliance with the extra requirements of Section 100100. It would also allow use of stem cell lines that may later be added to one of the approved registries, where the extra elements of 100100 were not included in the informed consents. Based on discussion with CIRM staff, my understanding is that this language accurately reflects CIRM's intent, and I am therefore hopeful that we will see it incorporated into the final version of the regulations: § 100100. Informed Consent Requirements. (a) All CIRM-funded human subjects research shall be performed in accordance with Title 45 Code of Federal Regulations, Part 46 (Protection of Human Subjects), revised June 23, 2005, and California Health and Safety Code section 24173. In accordance with existing law, California Health and Safety Code section 24173 does 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 Title 45 Code of Federal Regulations Part 46, revised June 23, 2005, and who obtains informed consent in the method and manner required by those regulations. (b) In addition to the requirements of 17 California Code of Regulations Section 100080, the following provisions apply	Revised language clarifies timing of regulations: *(b) In addition to the requirements of 17 California Code of Regulations Section 100080, the following provisions apply when CIRM funded research involves donation of gametes, embryos, somatic cells or human tissue or derivation of new covered stem cell lines which donation or derivation occurs after the effective date of this Chapter:*	3-102 WC034

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		when CIRM funded research involves donation of gametes, embryos, somatic cells or human tissue or derivation of new covered stem cell lines which donation or derivation occurs after the effective date of this Chapter: (1) CIRM-funds may not be used for research that violates the documented preferences of donors with regard to the use of their donated materials. The SCRO committee or IRB must confirm that donors of gametes, embryos, somatic cells or human tissue to be used to derive stem cell lines have given voluntary and informed consent in accordance with this section. To ensure donors are fully informed of the potential uses of donated materials, researchers shall disclose, in addition to the general requirements for obtaining informed consent identified in subdivision (a) of this regulation, all of the following, unless a specific item has been determined by the SCRO committee or IRB to be inapplicable. (1) a. Derived cells or cell products may be kept for many years. [*...And then also renumber the subsequent subsections -- those that are currently Sections 100100 (c) through (h) – so that they all are subsections of (b).* This would clarify the intent that the subsections that are now identified as (b) through (h) apply only in cases where the derivation (or the donation) occurs after the regulations are enacted, while ensuring that the "baseline" provisions of Section 100080 apply in all cases.]		
59	(b)(1)	We wholly support this provision that prohibits any violation of the preferences of the women who provide eggs for research. We would also add the importance of ensuring that women who provide eggs for research fully understand the informed consent and other documents. Therefore we propose adding a new last sentence in (b): The informed consent document(s) and any other written documents required under these regulations shall adhere to	This comment is effectively addressed in the existing regulations. Section 100100(a) cites California Health and Safety Code section 24173 by reference. *24173. As used in this chapter, "informed consent" means the authorization given pursuant to Section 24175 to have a medical experiment performed after each of the following conditions have been satisfied:* *(c) The subject or subject's conservator or guardian, or other*	2-91 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		simplified reading standards, including, but not limited to, those generally accepted and required for government publications, and in layperson's language. The document(s) shall be made available in languages spoken by subjects in the study if their proficiency is largely in a language other than English. All information in the written informed consent document shall also be conveyed to the subject orally in easy to understand and nontechnical terms.	*representative, as specified in Section 24175, is informed both verbally and within the written consent form, in nontechnical terms and in a language in which the subject or the subject's conservator or guardian, or other representative, as specified in Section 24175, is fluent, of the following facts of the proposed medical experiment, which might influence the decision to undergo the experiment..*	
	(b)(1)(A)	No direct comments		
	(b)(1)(B)	No direct comments		
60	(b)(1)(C)	Revise to clarify that if the cell lines are used for not yet known future studies, those future uses also will not violate the wishes of the woman who provided the eggs, and the researcher will be required to obtain informed consent for the new use. The proposed regulation creates an exception that ensures that subjects are *not* informed, and therefore violates and undermines the entire meaning of informed consent. We propose: (b)(3) Researchers may want to use cell lines for future studies, some of which may not be predictable at this time. Those future studies or uses may not violate the wishes of the providers of genetic materials, and the researchers must obtain informed consent for those uses at that future time.	Section 100100(b) describes the array of future uses of donated materials; consistent with the recommendations of the National Academies of Science. *In addition, donors could be offered the option of agreeing to some forms of hES cell research but not others. For example, donors might agree to have their materials used for deriving new hES cell lines but might not want their materials used, for example, for NT. The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored.* *To the extent possible, potential donors should be informed of the array of future research uses before giving consent to donate blastocysts for research. Comprehensive information should be provided to all donors that is readily accessible and at a level that will facilitate an informed decision. Written informed consent should be obtained from all those who elect to donate blastocysts or gametes.* It is a widely accepted practice to obtain consent to collect tissue for future research studies that cannot be predicted (e.g. biopsy tissue). Indeed the National Institutes of Health encourages its grantees to collect such samples for future research studies. Consistent with current practice the SWG specifically recommended that future	2-92 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
			consent not be required.	
	(b)(1)(D)	No direct comments		
	(b)(1)(E)	No direct comments		
	(b)(1)(F)	No direct comments		
	(b)(1)(G)	No direct comments		
	(b)(1)(H)	No direct comments		
61	(b)(1)(I)	The question of whether women who provide eggs for research may have any future rights is one that is being litigated in the courts, and may evolve over time. The regulations should therefore disclose whether the egg provider will receive any patent rights, rather than assume that the egg provider has no rights whatsoever. In addition, we propose the following additional language: This must be communicated to subjects in plain language, such as "The results of the research using your eggs may be patentable. If the researchers patent and profit from any discoveries they make using your eggs, they are not required to share those profits with you."	The language recommended in this comment is substantially similar to the existing language: *..the results of research may be patentable or have commercial potential, and that the donor will not receive patent rights and will not receive financial or any other benefits from future commercial development.* The regulations refrain from prescribing the exact language to be used in the informed consent process. The SWG chose to do this to allow researchers and IRBs to develop best practices regarding consent documents and discussions, based on empirical experience. Included but not limited to information from empirical evaluation mandated by 100100(d)(4).	
62	(b)(2)	(c) This provision that allows researchers to "cherry pick" only women who agree to all future uses of their eggs completely erases any sense of donor self-determination and makes a mockery of the rights of subjects in (b) above. There has been endless discussion at ICOC and Standards Working Group meetings about equality of opportunity for all women to provide eggs for research, yet this provision creates inappropriate pressure and coercion for women to forgo their own values and principles when they are faced with a researcher who says in essence, "if you don't agree to my terms, we don't want your eggs." We propose deleting the sentence, "Researchers may choose to use materials only from donors who agree to all future uses."	This provision applies to any donor of gametes, embryos or tissue which intended to derive covered stem cell lines. It is important to recognize that, at present, such lines do not have direct therapeutic value. Rather derived stem cell lines are building blocks for potential therapies. This circumstance is in contrast to other types of donations such as blood, bone marrow or whole organs where materials generally have direct therapeutic value when transplanted to recipients. To advance the therapeutic potential of derived stem cell lines, cells will be utilized in a variety of ways, including but not limited to those described in section 100100(b)(1-9). For some research, it will be impossible to prospectively anticipate the exact ways derived stem cell lines will be utilized. Further, the	2-93 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
			nature of the research is such that stem cell lines will need to be shared widely with other researchers; thus, placing them beyond the direct control of the researchers that performed the original derivation. The NAS anticipated that researchers would not be in a position at all times to adequately predict what the studies were going to be and, therefore would have to make a choice between limiting the usefulness of cell lines indefinitely into the future with all the record keeping complications as they moved around or having stem cell lines donated only with open-ended permission. There is no attempt in the NAS guidelines to discourage the creation of open-ended stem cell lines. Occasionally researchers may want to create lines with limited usefulness and they may do so with more restrictive consent. This provision received considerable discussion by the SWG and is considered the most effective means of simultaneously ensuring protection of participants' preferences while not creating untenable conditions for researchers and institutions and the carrying out of research that could benefit the public. See response to comment 7 regarding comment concerning selection bias by researchers.	
63		Documentation of donor preferences Re: future uses of donated materials may prove cumbersome and may add little given that subjects are already required to be informed of and to consent to research uses. Researchers are, appropriately, already being required to inform potential donors of anticipated research uses, and can only conduct funded research using materials from donors who give voluntary informed consent. The draft regulations explicitly permit a researcher to choose to use materials only from donors who consent to all future uses. Given that, it is unclear what is added by an additional requirement that researchers obtain (and presumably retain) additional information about a donor's	This section is intended to provide donors the opportunity to identify any specific preferences. Such information may be valuable if materials are shared with other researchers.	2-61 WC017-3

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		preferences regarding specific uses that may not even be relevant (e.g., if a researcher chooses to use materials only from donors who consent to all future uses, is there utility in requiring documentation and retention of specific donor use preferences?).		
64		Previous comments expressed concern that Section 100100(c) (requiring documentation of donor preferences regarding future uses of donated materials) could prove cumbersome and may add little or no protection given that subjects already are required to be informed of, and to consent to, research uses. It continues to be unclear what is added by a requirement that researchers obtain (and presumably retain) additional information about a donor's preferences regarding specific uses that may not even be relevant (e.g., if a researcher chooses to use materials only from donors who consent to all future uses, is there utility in requiring documentation and retention of specific donor use preferences?).	This section is intended to provide donors the opportunity to identify any specific preferences. Such information may be valuable if there are identified restrictions on materials and researchers intended to share materials. The provision is intended to ensure any restrictions are documented during original procurement process.	3-106 WC034
	(b)(3)	No direct comments		
65	(b)(3)(A)	This provision ignores the most severe potential risks of ovarian stimulation for multiple egg extraction and therefore is misleading to potential egg providers and undermines the principles of informed consent. As Drs. David Magnus and Mildred Cho recommend, the risks of hospitalization, renal failure, infertility and death must be disclosed. Magnus and Cho, "Issues in Oocyte Donation for Stem Cell Research," Science Express 19 May 2005, and "A Commentary on Oocyte Donation for Stem Cell Research in South Korea", The American Journal of Bioethics 6(1):W 23 (2006). We also believe women must be informed that there are methods of providing eggs that do not involve pharmaceutically induced ovarian stimulation. We proposed the following revision: (1) The description of foreseeable risk shall include but not be	Oocyte retrieval is carried out under anesthesia. The risk of death is routinely discussed as part of the consent process for anesthesia. At this time, the risk of hospitalization will need to be discussed as part of the discussion of the risk of hyperovulation syndrome. We have chosen not to require a lengthy list of specific disclosure requirements that are redundant with disclosure requirements already imposed as a matter of the "reasonable physician" standard required for disclosure in California. Not all possible risks should be specified as required in regulations. The association between hormonal stimulation for oocyte donation and infertility and other medical risks will be discussed at the forthcoming symposium on the medical risks of oocyte donation organized by the Institute of Medicine with CIRM sponsorship. The SWG received information from scientists that although there is suggestive animal data, the situation in human beings is not well established. Similarly, methods of providing oocytes without	2-96 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		limited to information regarding the risks of ovarian hyperstimulation syndrome, bleeding, infection, anesthesia, pregnancy, renal failure, infertility, hospitalization and death. Insert a new (2) (and subsequent renumbering) The physician must disclose that there are methods of providing oocytes for research that do not involve pharmaceutically induced ovarian stimulation, and a description of those methods.	ovarian stimulation are not established practice.	
66		Requires that a "…description of foreseeable risks shall include but not be limited to information regarding the risks of [OHSS], bleeding, infection, anesthesia, and pregnancy." This is an important requirement that appears to confuse pregnancy with fertility by implying that pregnancy is a risk of OHSS. I could not find such a risk in the relevant literature. Is it possible the intent is to describe a risk of future infertility due to OHSS? If so, the statement should be appropriately revised. **RECOMMENDATION:** Change the phrase "…risks of… pregnancy" to "…risks of… future infertility". *CIRM Proposed Medical and Ethical Standards, CA Code of Regulations* page 6	Infertility is not a documented risk and donors do need to know that they can become pregnant after oocyte retrieval. Provision should remain and clarification may be provided in the future for pregnancy.	3-117 WC036
	(b)(3)(B))	No direct comments		
67	(b)(3)(C)	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?	SWG considered at 5/3/06/06 meeting, language was revised regarding opportunity to deliberate, addressed in comment 68, but SWG felt it was important to require recontact to be initiated by potential participants.	2-61 WC017-6
68		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. However, in this effort to enhance informed consent the regulations requires a "deliberative" period in the consent process. Unfortunately, in the reproductive rights field, a	SWG considered at 5/3/06 meeting, language was revised to read: *Prospective donors shall be informed of their option to deliberate before deciding whether or not to give consent. If a deliberation period is chosen, the researchers may not re-contact the prospective donor about the consent decision.* The SWG considered at 5/3/06 meeting language to authorize re-	2-62 WC020 WC021 WC029 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		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 potentially undermining existing rights. Such a provision may not be necessary. There is already sufficient time to consider the decision to donate with the proposed informed consent process. (4)(vi) should be consistent with (b)(2) that states that women who provide eggs can only be recontacted if they have so agreed at the time their eggs are procured.	contact at time of consent. The SWG maintained concerns that re-contact may introduce pressure, and retained the provision to prohibit re-contact. SWG were persuaded by testimony from research centers recruiting oocyte donors that loss-to-follow-up is a minor problem. The SWG indicated a willingness to revisit this provision at a future date if necessary.	
69		Restriction on recontacting donors after required "deliberation" period could unduly inhibit subject recruitment without significantly enhancing protection for subjects. 100100(d)(3) prohibits researchers from soliciting potential donors until the donors have themselves initiated recontact with the researchers after the requisite "deliberation period." This requirement could unduly inhibit the effectiveness of subject recruitment while offering little or no added protection to subjects. Researchers should have some opportunity to follow up with potential participants. Potential donors who do, indeed, want to participate, may, nonetheless be busy and forget to make a phone call; it seems reasonable to give researchers an opportunity to contact them to determine whether, after consideration, they have decided to participate in the research. Could the intent of this provision be accomplished by requiring the researchers to wait a minimum time period before recontacting potential participants?	SWG considered comment at 5/3/06/06 meeting. SWG decided as a matter of policy that donor should initiate re-contact consistent with language above (comment #68). See comments #70-71.	2-69 WC017
70		We appreciate changes made to Section 100100 (d) relative to a deliberation period before a donor makes her decision to donate. The new language is indeed an improvement. However, due to the sensitivity of this issue in a reproductive health context, we still believe the language still goes further	Language revised to read: *(C) Prospective donors shall be informed of their option to deliberate before deciding whether or not to give consent. If a deliberation period is chosen, the donor shall be informed of their*	3-100 WC033

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		than is necessary. Given the context, we are being very particular about the language. We suggest language that would say "a prospective donor shall be informed that for this and any procedure (to make it clear this is nothing new...anyone can step back from a procedure and say they would like additional time), the donor may opt for additional time to do further research or inquiry as to the details of the procedure. Should the donor opt for additional time, the donor should be asked her preference as to how recontact will be made, if any, between the donor and the researchers."	*right to determine the method of recontact. The donor must be informed that they have the option to initiate recontact. The investigators shall not initiate recontact unless the donor has consented, and this consent is documented in the research record.*	
71		The May 9 revisions to Section 100100(d)(3) provide that if a potential donor chooses to deliberate prior to consenting to donate, researchers are prohibited from recontacting a potential donor about their consent decision. This could unnecessarily restrict recruitment without meaningfully enhancing subject protection. Researchers should have some opportunity to follow up with potential donors while still respecting any decision to choose a deliberation period. Certainly, potential donors should not be subjected to harassment or pressure, but respectful follow-up is neither of those things, and it is unclear why it should be prohibited here when it is standard and permissible in other areas of subject recruitment. The intent to ensure respect for donor preferences regarding re-contact could be accomplished by making the following modification: Section 100100(d) (3). Prospective donors shall be informed of their option to deliberate before deciding whether or not to give consent. If a deliberation period is chosen, the methodology and timing of recontact by investigators should be prospectively discussed with and agreed upon with the potential donor, and documented in the research records. Researchers may not recontact the prospective donor about the consent decision.	Language revised to read: *(C) Prospective donors shall be informed of their option to deliberate before deciding whether or not to give consent. If a deliberation period is chosen, the donor shall be informed of their right to determine the method of recontact. The donor must be informed that they have the option to initiate recontact. The investigators shall not initiate recontact unless the donor has consented, and this consent is documented in the research record.*	3-106 WC034

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		"If a deliberation period is chosen, the researchers may not recontact the prospective donor about the consent decision." Though there is agreement that investigators should not harass potential donors, the regulation should, (a) not unduly restrict donor autonomy in choosing the contact methodology the donor would prefer regarding further discussion after deliberation, (b) not preempt IRB decision making on individual research applications that may warrant approval of alternative recruitment strategies, and (c) provide additional protections based on documented scientific evidence of potential harms or inconvenience that pose greater than minimal risk to the donors rather than speculation. ***Recommended Change*** My recommended change is based on the following: 1. Follow-up contact poses no greater than minimal risk to the potential donors, 2. A donor's preference to deliberate on the possibility of donation should be respected but also should not be assumed to be a negative response or rejection of the research. Instead, the regulation should be neutral in its assessment of the reason a donor may choose a deliberation period, promote women's autonomy, and avoid paternalistic restrictions based on speculative harms, and 3. IRBs should be allowed to do their job, that is, assess the potential risks and benefits based on the individual proposal rather than CIRM promulgating global unjustified restrictions. 4. The recommended change accommodates CIRM's requirement that potential oocyte donors have time and space for the deliberation process while ensuring that women are provided legitimate protections, IRBs review and approve an appropriate contact methodology that demonstrates respect for the individual woman, and the process empowers the woman's decision making: a. the potential donor and investigator should engage in a discussion about recontact,	Language revised to read: *(C) Prospective donors shall be informed of their option to deliberate before deciding whether or not to give consent. If a deliberation period is chosen, the donor shall be informed of their right to determine the method of recontact. The donor must be informed that they have the option to initiate recontact. The investigators shall not initiate recontact unless the donor has consented, and this consent is documented in the research record.*	3-117 WC036

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		b. determine an appropriate methodology and timeline for the contact, if any, and c. require that the investigator document the discussion and agreement in the research records. **RECOMMENDATION:** "If a deliberation period is chosen, the methodology and timing of recontact by investigators should be prospectively discussed with and agreed upon with the potential donor, and documented in the research records." *CIRM Proposed Medical and Ethical Standards, CA Code of Regulations* page 7 *Real v. Speculative Harms* Current Federal and state human research regulations do not prohibit investigators from recontacting potential subjects who expressed interest in research. IRBs also currently have the authority to require such a restricted process when appropriate, that is, when such contact may result in documented potential harms. Therefore, IRBs regularly make such decisions about access, when warranted, and on a case-by-case basis rather than implementing blanket policies that will unduly restrict all research. Interestingly, contrary to the CIRM "Initial Statement of Reasons" federal and state human research regulations for clinical research that poses more risk to human subjects than oocyte donation research do NOT reflect this proposed CIRM standard. CIRM should allow IRBs to perform their duties, that is, negotiate on a case-by-case basis the appropriate protection of research subjects based on the context of the proposed research. Without justification of the restriction through scientific literature documenting harms resulting from contact, the Standards Working Group will create regulation based on speculative harms resulting in unjustified, unnecessary, and unwarranted restrictions on the autonomy and dignity of the subjects. *Lack of Clarity* The regulation as currently drafted presumes that a "consent decision" occurred when the donor may have only asked for time to deliberate further without necessarily declining to		

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		donate for the research. A reasonable person, therefore, could interpret the regulation as providing additional protections only for women who initially refuse donation. Thus the regulation would allow investigators to recontact potential donors who upon initial contact did not decline donation but rather only asked for additional time to deliberate about a future decision.		
72	(b)(3)(D)	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.	Language revised to read: *The researcher shall ascertain that the donor has understood the essential aspects of the research, following a process approved by the designated IRB or SCRO committee*.	2-59 WC016-2
	(D)(i-viii)	No direct comments		
73	100100(e)	It is possible that in future human ES cell derivations may not require destruction of embryos (e.g. Chung et al. Nature 439:216, 2006).	In Section 100100(b) there is a provision allowing the SCRO committee or IRB to determine a specific consent item is inapplicable. This precedent could be extended to other sections as the need arises.	2-74 WC025
74	(f)(g)	Existing cord blood donation only requires mother consent.	Final language revised on advise from ICOC on 6/2/06 to read: *(6) <u>For CIRM-funded research that uses the umbilical cord, cord blood or the placenta, consent shall be obtained from the birth mother.</u>*	2-58 WC014
75		The requirement that consent be obtained from "each known legal parent, guardian, or progenitor" is contrary to standard practice and raises unnecessary questions of constitutionality. This provision should be eliminated. There is no such thing as a legal parent of an umbilical cord, cord blood, or a placenta. Moreover, the concept of "progenitor" is unknown in the law, and only invites confusion and litigation. The National Marrow Donor Program obtains consent from the woman only. The National Academies recommendations for cord blood donations recognize that few cord blood banks obtain	Final language revised on advise from ICOC on 6/2/06 to read: *(6) <u>For CIRM-funded research that uses the umbilical cord, cord blood or the placenta, consent shall be obtained from the birth mother.</u>* SWG engaged in extensive deliberation at 5/3/06 meeting (see public record) and recommended the following language: *For CIRM-funded research that uses umbilical cord, cord blood or*	2-94 WC022 WC028

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		consent from both parents, and they identify both practical and conceptual difficulties in obtaining consent from a woman and a man. "The committee does not advocate requiring the father's consent." Instead, the guidelines suggest a plan for addressing paternal objections should they occur. A requirement of consent from both a woman and man could potentially involve the research institution in unnecessary litigation over the determination of who the second parent actually is. In the case of abortion, establishing a protocol requiring male consent for a woman to dispose of the byproducts of her pregnancy is both flatly inconsistent with existing law giving women alone the right to decide whether to terminate a pregnancy, and is likely to lead to litigation, cost, delay, and deterrence of donations. It will almost certainly deter women who choose to terminate pregnancies without disclosing them to their partners, as they are constitutionally permitted to do. This provision not only violates a woman's privacy right to choose abortion and medical care, but also her right to informational privacy. We propose the following revision: (f) For CIRM-funded research involving the donation of the umbilical cord, cord blood or the placenta, consent shall be obtained from the pregnant woman.	*the placenta for autologous donation or for purposes other than derivation of covered stem cell lines, consent shall be obtained from the woman giving birth. -For CIRM-funded research that uses umbilical cord, cord blood or the placenta to derive covered stem cell lines for purposes other than autologous donation, in order to assure scientific rigor, consent shall be obtained from each legal parent, guardian and genetic parent. Nothing in this section shall be construed to affect state or federal law with regard to consent in reproductive decision making.*	
76		We continue to have concerns about the broad requirements as to who must give consent to the provision of umbilical cord, cord blood, and placenta materials. We still believe that the constitution and current practice as noted by the National Marrow Donor Program and the National Academies, require that consent should only be required from the pregnant woman. We reiterate our concerns that, at the very least, no one other than genetic contributors should be required to give consent. Neither legal parents nor guardians necessarily have	Final language revised on advise from ICOC on 6/2/06 to read: *(6) <u>For CIRM-funded research that uses the umbilical cord, cord blood or the placenta, consent shall be obtained from the birth mother.</u>*	3-112 WC032 WC035

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		any genetic link to the tissue in question, and their consent serves neither a scientific rigor nor a privacy goal. Last, we repeat our objection to the term "genetic parent" as it lacks clarity, can easily be confused with legal parent, and again does not achieve the goals of this section. If, however, it is decided that for the purpose of scientific rigor and the privacy rights of tissue donors, consent should be obtained from anyone other than the pregnant woman, we propose: The phrase "genetic parent" should be replaced with "genetic contributor" in (f) and (g) *(f) . . . . . For CIRM funded research that uses umbilical cord, cord blood or the placenta to derive covered stem cell lines for purposes other than autologous donation, in order to assure scientific rigor, consent shall be obtained from each genetic contributor. Nothing in this section shall be construed to affect state or federal law with regard to consent in reproductive decision-making.* *(i) The pregnant woman shall be informed in writing during the first conversation about donation that (a) donation requires disclosure of the names and contact information of all genetic contributors; and (b) donation requires that genetic contributors be contacted in order to secure their informed consent. Under no circumstances shall a genetic contributor who is not the pregnant woman be contacted if the pregnant woman has not given written informed consent for such contact.*		
77		The Section requires informed consent from "each legal parent, guardian, and genetic parent" for the donation of umbilical cord, cord blood, or placenta for stem cell research other than autologous donation. The reasoning for this regulation appears misplaced and scientifically incorrect.	Final language revised on advise from ICOC on 6/2/06 to read: *(6) For CIRM-funded research that uses the umbilical cord, cord blood or the placenta, consent shall be obtained from the birth mother.*	3-119 WC036

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		Additionally, the regulation is overly restrictive, inconsistent with current Federal and State regulations for such donation, inconsistent with current standard research and clinical practices for such donation, appears to provide the biological material the same legal status as a fetus, and creates a new category of research donor: "guardian" of the material. a. If the requirement is based on a concern that the umbilical cord, etc., is the father's genetic material similar to sperm, the concept is not supported in the scientific literature. The umbilical cord, etc., propagates the genome of the fetus/baby and is not the father or the father's genetic material anymore than the blood of an adult child is the father's genetic material. An analogy would be CIRM requiring the informed consent of a father for his adult child to donate biological material, such as blood for stem cell research, based on the premise that the father has a right to make such decisions and trump the wishes of an adult child because the blood is composed of the father's genetic material. Therefore, informed consent for the donation of umbilical cords, etc., should be obtained from the woman and the proposed additional consent requirements should be omitted. b. The CIRM informed consent requirement is overly restrictive and poses real potential harm to future research. The regulation should mirror the current widely accepted cord blood bank model. Research and clinical cord blood banking policies do **NOT** require the informed consent of the genetic father. CIRM regulations should be consistent with current banking policies or run the risk that current and future banked materials will not be available for stem cell research, resulting in an unnecessary and unfounded restriction on stem cell science. c. The section indicates that the informed consent requirements are to assure the research has appropriate "scientific rigor." It is unclear how the informed consent requirements "assure scientific rigor" of a proposed research		

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		protocol. Though informed consent requirements may contribute to the ethical quality of the donation, it is difficult to understand how such requirements will assure scientific rigor. If the basis for the requirement is the promotion of scientific rigor than CIRM should directly address umbilical cord, etc., science rather than place undue restrictions on a woman's right to choose the ultimate disposition of her bodily materials. d. Umbilical cord, etc., is not the same as a fetus and should not be provided more regulatory protections than a fetus. Federal research informed consent regulations for the collection of placenta, etc., do not require informed consent from the "father" [45 CFR 46.206(a)] for the donation of such material for research. e. The revised Section indicates informed consent for such donation requires the informed consent of "each legal parent, guardian, ***and*** genetic parent [emphasis added]." The use of the term "parent" is misleading as there are no parents of the umbilical cord, etc., and incorrectly equates the biological material with a fetus or baby. It is unclear why the CIRM is creating rights for all of the listed groups "legal parent, guardian, ***and*** genetic parent" that are superior to and trump the mother's fundamental legal right to provide informed consent for donation of her bodily material. It is also unclear what the Working Group means by the "guardian" of the umbilical cord, etc., or why the Group would create a new category of research donor. Who would be the "guardian" of such biological material? How is that guardianship determined and under what authority? If the intent of the Section is to ensure that a guardian of the baby or nongenetic parent has the authority to make donation decisions; it is equally unclear why the Group would want to deny the legal authority of the mother to donate her bodily materials for stem cell science as she sees fit without intrusion		

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		from others. **RECOMMENDATION:** Revise the sentence to require only the informed consent of the woman: "For CIRM-funded research that uses umbilical cord, cord blood, or the placenta to derive covered stem cell lines for purposes other than autologous donation, in order to assure scientific rigor, consent shall be obtained from the woman each legal parent, guardian, and genetic parent."		
	(h)	No direct comments		
	S 100110	**Fairness & Diversity in Research**		
	100110	No direct comments on this section		
	S 100120	**Record Keeping**		
78	General	Data collection is an important aspect of accountability, monitoring, enforcement, and quality. Only with good data collection and review will the ICOC and the public be able to effectively evaluate this new science as it moves forward. We propose adding the following records to be kept: (e) summaries of proposed research activities that went before the SCRO and the IRB, and whether they were approved. (f) policies and procedures adopted by the SCRO. (g) an overview of any human stem cell research being done at the institution that is *not* following CIRM standards. (h) an overview of any failures to comply with these standards. (i) The demographics of the providers of oocytes or embryos used in the derivation of each cell line. (j) A summary of results, both positive and negative, of any CIRM-funded research or clinical trial. (k) Any significant adverse reactions in a clinical trial. (l) A disclosure of the personal, professional, and financial interests in biotechnology or biomedical companies of the SCRO members.	The SWG and public engaged in substantial discussion about reporting requirements at the 5/3/06 meeting. The SWG indicated that detailed reporting requirements were outside the intended scope of these regulations. CIRM staff emphasized that many of records alluded to in this comment are required in whole or part in the CIRM Grants Administration Policy (GAP). The GAP will be noticed with the OAL. There was a commitment from CIRM and the SWG co-chairs to consider reporting requirements in future deliberations. Such deliberations need to be informed by the GAP and should occur in consolation with CIRM Grants Administration staff.	2-97 WC022

#	Section	Summary of Public Comment(s)	Response to Public Comment	Ref.
		(m) health outcomes of oocyte donors resulting from oocyte retrieval, including adverse health reactions resulting from ovarian stimulation. As commented above for Section 100040, these records should be available to the public, with exceptions for the privacy of any patient who may be personally identifiable, or for proprietary intellectual property.		
	(a-f)	No direct comments on these sections		
	S 100130	**Materials Sharing**		
	100130	No direct comments on this section		