Summary: Original Basis for CIRM MES Regulations

Prepared for ICOC Consideration 08/02/06

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S 100010	Issue	Source	Comment	Reference
S 100020	**Issue**	**Source**	**Comment**	**Reference**
(a)	Acceptably derived	SWG	Section 100080, defines conditions for acceptable research materials. Authority derived from CA H&S code 125290.35 (b) The **ICOC** shall establish standards as follows: (1) informed consent, (2) controls on research involving humans, (3) prohibition on compensation, (4) patient privacy laws (5) limitations on payments for cells, (6) time limits for obtaining cells.	CA_H&S_12590.55 (b)(2)
(b)	CIRM	P71	California Institute for Regenerative Medicine: Authorized by Article 35: Section 1. There is hereby established the California Institute for Regenerative Medicine.	CA Constitution XXXV
(c)	Covered stem cell line	SWG	SWG intended to capture relevant materials and activities not currently covered by existing regulations or oversight guidelines, see Working Notes 7. Definition revised and modified in response to public comment.	Working_Notes_7 WC_018
(d)	Funded research	P71	Authorized by Article 35: SEC. 2. The institute shall have the following purposes: (a) To make grants and loans for stem cell research, for research facilities, and for other vital research opportunities to realize therapies, protocols, and/or medical procedures that will result in, as speedily as possible, the cure for, and/or substantial mitigation of, major diseases, injuries, and orphan diseases. see: *Interim CIRM Grants Administration Policy for Academic and Non-Profit Institutions*	CA Constitution XXXV Interim_GAP
(e)	Human Subject	HHS	From the Federal Common Rule.	45CFR Part 46
(f)	Institution	HHS	From the Federal Common Rule.	45CFR Part 46
(g)	IRB	HHS	Intuitional Review Board: From the Federal Common Rule.	45CFR Part 46
(h)	Permissible expenses	P71 & SWG	Authority derived from 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." see: *Interim CIRM Grants Administration Policy for Academic and Non-Profit Institutions.*	CA_H&S_Code_125290.35(b)(3) SWG 01/30/06 Transcript P205.L24 Interim_GAP
(i)	Research	HHS	From the Federal Common Rule.	45CFR Part 46
(j)	(SCNT)	NIH	Somatic Cell Nuclear Transfer: Modified definition from *NIH Report on Stem*	NIH_Appendix_F

			Cells appendix F. Modifications based on public comment.	SWG_05/03/06_#2
(k)	SCRO committee	NAG	Stem Cell Research Oversight committee: Based on NAG recommendation. SCRO committee review described in section 100070.	NA Guidelines 2.0
S 100030	**Issue**	**Source**	**Comment**	**Reference**
(a)	Human reproductive cloning	P71 & NAG	Article 35 Section: No funds authorized for, or made available to, the institute shall be used for research involving human reproductive cloning. "human reproductive cloning" is defined in P71. NAG recommended that "Human reproductive cloning should not now be practiced. It is dangerous and likely to fail."	CA Constitution XXXV H&S Code 125292.10 NA Guidelines 1.1(b)
(b)	12 day limit on culture of embryo	P71 & NAG	NA Guidelines have a 14 day limit, P71 sets limit of "12 days after cell division begins."	H & S Code 125290.35(b)(6)
(c)	Stem cells into primate embryos	NAG	Direct recommendation of NAG.	NA Guidelines 1.2(c)(2)
(d)	Stem cells into human embryos	NAG	Direct recommendation of NAG.	NA Guidelines 1.2(c)(2)
(e)	Breeding animals with human stem cells	NAG	Direct recommendation of NAG.	NA Guidelines 1.2(c)(3)
(f)	Implanting genetically modified embryo	SWG	Provision added in response to public concern that research will result in inheritable genetic modification of human beings.	SWG 05 03 06 Transcript P 224.
S 100040	**Issue**	**Source**	**Comment**	**Reference**
(a)	Designate responsible official	NAG	"All scientific investigators and their institutions, regardless of their field, bear the ultimate responsibility for ensuring that they conduct themselves in accordance with professional standards and with integrity."	NA Guidelines 1.3
(b)	Designate SCRO	NAG	"To provide oversight of all issues related to derivation and use of hES cell lines and to facilitate education of investigators involved in hES cell research, each institution involved in hES cell research should establish an Embryonic Stem Cell Research Oversight (ESCRO) committee." Provision amended to require chancellor, CEO, or person with plenary authority to designate responsible official.	NA Guidelines 2.0 WC030 #2
(c)	Designate IRB	NAG & CA	"An IRB, as described in federal regulations at 45 CFR 46.107, should review the procurement of all gametes, blastocysts, or somatic cells for the purpose of	NA Guidelines 3.1 H & S Code 125300(b)

			generating new hES cell lines." Consistent with CA Health & Safety Code 125300(b).	
(d)	Conscientious objection	NAG	"Clinical personnel who have a conscientious objection to hES cell research should not be required to participate in providing donor information or securing donor consent for research use of gametes or blastocysts."	NA Guidelines 3.7
S 100050	**Issue**	**Source**	**Comment**	**Reference**
(a-h)	Compliance	NIH	These provisions are modeled after NIH policy and contained in CIRM Grants Administration Policy.	NIH Policy 12_03 Interim_GAP_p._36
S 100060	**Issue**	**Source**	**Comment**	**Reference**
(a)	SCRO membership	NAG	"The committee should include representatives of the public and persons with expertise in developmental biology, stem cell research, molecular biology, assisted reproduction, and ethical and legal issues in hES cell research." Provisions regarding non-scientist member, permissible expenses, and financial interest added in response to comments.	NA Guidelines 2.0 SWG_05/03/06_#4 WC030_#3 WC022
(b)	SCRO function	NAG	"It must have suitable scientific, medical, and ethical expertise to conduct its own review and should have the resources needed to coordinate the management of the various other reviews required for a particular protocol."	NA Guidelines 2.0
(c)	SCRO investigator education	NAG	The ESCRO should facilitate education of investigators involved in hES [stem] cell research.	NA Guidelines 2.0(5)
(d)	SCRO for two or more institutions	SWG	Commentators indicated it may be difficult for all institution to have the necessary expertise or it may not be economical for small institutions or programs to establish independent committees.	Public Session 03 12/14/05 Workshop SWG 10/24/06 Transcript P105.L7
(e)	SCRO may be convened by group of institutions or state agency	SWG	Based on rationale in 100005(d); and the desire to explicitly enable multiple options for research oversight.	SWG 10/24/05 Transcript P90.L23
S 100070	**Issue**	**Source**	**Comment**	**Reference**
(a)	Procurement & use of oocytes	NAG/ SWG	Procurement or use of oocytes is an ethically sensitive issue requiring review. SWG is charged with recommending "safe and ethical procedures for obtaining materials and cells for research."	NA Guidelines 3.0 CA_H&S_12590.55 (b)(2)

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				SWG_05/03/06_#3
(a)(1)	Acceptable scientific rationale	NAG/ SWG	Procurement of oocytes involves risk to donors; an acceptable scientific rational should be provided for such research.	NA Guidelines 4.4
(a)(2)	Demonstrate expertise	NAG	"Research teams should demonstrate appropriate expertise or training in derivation or culture of either human or nonhuman ES [stem] cells"	NA Guidelines 4.3
(a)(3)	Document compliance with necessary review	NAG	"An IRB, as described in federal regulations at 45 CFR 46.107, should review the procurement of all gametes, blastocysts, or somatic cells for the purpose of generating new hES cell lines…"	NA Guidelines 1.2 NA Guidelines 3.1
(b)	Use of human embryos	NAG/ SWG	Use of embryos is an ethically sensitive issue requiring review.	CA_H&S_12590.55 (b)(2)
(b)(1)	SCRO approval for CIRM-funded derivation	NAG	Embryo research is ethically sensitive; an acceptable scientific rational should be provided for such research.	NA Guidelines 4.2 & 4.4
(b)(2)	Demonstrate expertise	NAG	"Research teams should demonstrate appropriate expertise or training in derivation or culture of either human or nonhuman ES [stem] cells"	NA Guidelines 4.3
(b)(3)	Document compliance with necessary review	NAG	"An IRB, as described in federal regulations at 45 CFR 46.107, should review the procurement of all gametes, blastocysts, or somatic cells for the purpose of generating new hES cell lines…"	NA Guidelines 1.2 NA Guidelines 3.1
(c)	Derive covered stem cell line	NAG/ SWG	Scientific rationale for generating new ES [stem] cell lines, is required.	NA Guidelines 4.0
(c)(1)	Acceptable scientific rationale	NAG/ SWG	The scientific rationale for the need to generate new ES [stem] cell lines, by whatever means, must be clearly presented.	NA Guidelines 4.0
(c)(2)	Justify SCNT	NAG/ SWG	SCNT requires oocytes so use should be justified.	NA Guidelines 4.2
(c)(3)	Demonstrate expertise	NAG	"Research teams should demonstrate appropriate expertise or training in derivation or culture of either human or nonhuman ES [stem] cells"	NA Guidelines 4.3
(c)(4)	Document compliance with necessary review	NAG	"An IRB, as described in federal regulations at 45 CFR 46.107, should review the procurement of all gametes, blastocysts, or somatic cells for the purpose of generating new hES cell lines…"	NA Guidelines 1.2 NA Guidelines 3.1
(c)(5)	Document how cell lines will be characterized	NAG	"Investigators must document how they will characterize, validate, store, and distribute any new hES cell lines."	NA Guidelines 4.6
(d)	Notify in vitro	NAG	Purely *in vitro* hES cell research is permissible after notification of the	NA Guidelines 1.2(a)

	research		research institution's ESCRO committee and completion of the reviews mandated by current requirements.	
(d)(1)	Cell lines are acceptably derived	NAG	Requirement is applicable to all cell lines used by researchers. To be considered "acceptably derived" cells must conform to requirements 100080.	NA Guidelines 3.1-3.4(b)
(d)(2)	Document compliance with necessary review	NAG	Consistent with 100070(b)(3).	NA Guidelines 1.2(a)
(e)	Introduction of stem cells to animals	NAG	Research involving the introduction of hES cells into nonhuman animals at any stage of embryonic, fetal, or postnatal development. Introduction of neural-progenitor cells to the brain identified as category of research that merits special review.	NA Guidelines 1.2(b)(2) SWG 01/30/06 Transcript P61.L6 SWG 05/03/06 P103. L10
(e)(1)	Acceptable scientific rationale	NAG	All protocols involving the combination of hES cells with nonhuman embryos, fetuses, or adult animals must be submitted to the local IACUC for review of animal welfare issues and to the ESCRO committee for consideration of the consequences of the human contributions to the resulting chimeras.	NA Guidelines 6.4-6.5
(e)(2)	Cell lines are acceptably derived	NAG	Requirement is applicable to all cell lines used by researchers.	NA Guidelines 3.1-3.4(b)
(e)(3)	Evaluate probable pattern of differentiation	NAG/ SWG	"particular attention should be paid to the probable pattern and effects of differentiation and integration of the human cells into the nonhuman animal tissues."	NA Guidelines 1.2(b)(2) NA Guidelines 6.4-6.5
(e)(4)	Document compliance with necessary review	NAG	Consistent with 100070(b)(3).	NA Guidelines 1.2 NA Guidelines 3.1
(f)	Introduction of stem cells to humans	SWG	SWG extended NAS recommendations reflected in section 100070(e) to humans. Such research requires IRB review, the SCRO committee review with expertise in stem cell research can inform IRB deliberations. Consistent with NAS recommendation that the SCRO committee provide oversight for all issues related to derivation and ***use*** of stem cell lines.	
(f)(1)	Acceptable scientific rationale	SWG	The NAS recommends that the SCRO committee provide an additional level of review and scrutiny warranted by the complex issues raised by hES cell research.	NA Guidelines 2.0
(f)(2)	Cell lines are	SWG	Requirement is applicable to all cell lines used by researchers.	NA Guidelines 3.1-3.4(b)

	acceptably derived			
(f)(3)	Evaluate probable pattern of differentiation	SWG	Consistent with protection of human subjects / Common Rule	45CFR Part 46
(f)(4)	Document compliance with necessary review	SWG	Constitutes human subjects research must comply with Common Rule	45CFR Part 46
(g)	Appeals of SCRO decision	SWG	Comments indicated a specific need for appeals authority.	WC_030_#7
(h)	SCRO Renewal		Comments indicated a specific need for renewal language.	WC_030_#4 WC_034_B_2
S 100080	**Issue**	**Source**	**Comment**	**Reference**
(a)(b)(c)	NIH approved lines	SWG	The NIH, HFEA, and UK stem cell lines view as equivalent. HFEA Code of Practice consistent with requirements of 100080(e).	SWG 8/30/05 Transcript P102.L22 HFEA_Decision_Tree UK_Policy
(d)	CIHR licensed lines	SWG	CIHR license requirements meet standard discussed by SWG.	CIHR_Guidelines
(e)(1)	Voluntary & informed consent	HHS & NAG	Fundamental protection under Federal law & major recommendation of NA.	45CFR Part 46 NA Guidelines 3.1
(e)(2)	Donors did not receive valuable consideration	P71 & NAG	The ICOC shall establish "standards prohibiting compensation to research donors or participants, while permitting reimbursement of expenses." Reimbursement standard developed by SWG on 12/30/06.	CA_H&S_Code_125290.35(b)(3) SWG 01/30/06 Transcript P205.L24&P220.L9
(e)(3)	Persons did not receive valuable considerations	P71, ICOC	Provision intended to make prohibition on compensation consistent with 100080(e)(2). H&S Code 125290.35(b)(5): "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."	CA_H&S_Code_125290.35(b)(5) ICOC_2_10_06_#3 CA_H&S_Code_125290.35(b)(3) &_(5) CA_H&S_Code_125320_(b)

(e)(4)	Donation overseen by IRB	HHS, NAG & CA	IRB responsible for ensuring fundamental protection under Federal law & major recommendation of NA. Consistent with existing state regulation where IRB oversees aspects of donation of gametes, embryos and tissue.	45CFR Part 46 NA Guidelines 3.1 CA H&S Code 125300
(e)(5)	No compensation for storage costs	NAG	"People who elect to donate stored blastocysts for research should not be reimbursed for the costs of storage prior to the decision to donate."	NA Guidelines 3.4(a)
S 100090	**Issue**	**Source**	**Comment**	**Reference**
	Additional requirements for CIRM derivation	P71/SWG	Additional requirements adapted for CIRM-funded derivation consistent with CA H&S code 125290.35(b)(1): (b) The **ICOC** shall establish standards as follows: (1) Informed Consent Standards for obtaining the informed consent of research donors, patients, or participants, which initially shall be generally based on the standards in place on January 1, 2003, for all research funded by the National Institutes of Health, with modifications to adapt to the mission and objectives of the institute.	CA H&S Code 125290.35 (b)(1)
S 100095	**Issue**	**Source**	**Comment**	**Reference**
(a)	SART certified	SWG	SART certification intended to ensure standard of care for oocyte donors.	SWG 05/03/06 #16
(b)	Shall not knowingly compromise optimal reproductive success	SWG	Provision intended to provide additional protections to prospective donors. Sections (b)(1) and (b)(2) describe consent process for donating materials for research that are not otherwise needed for reproductive success (e.g. failed to fertilize oocytes/embryos).	SWG Briefing Memo 7 19 06 SWG_07/19/06
(c)	Medical care provided at no cost to donor	SWG	Provision intended to provide economic protections to prospective donors.	SWG 01/30/06 Transcript P218.L9 SWG 05/03/06 #8
(d)	Physician and PI not the same individual	NAG	"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."	NA Guidelines 3.5
(e)	Physician not have financial interest in research outcome	SWG	Provision intended to protect prospective donors from undue influence.	SWG 01/31/06 Transcript P325.L12 & SWG 01/31/06 Transcript P347.L11
S 100100	**Issue**	**Source**	**Comment**	**Reference**

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(a)	Informed consent requirements	NAG, SWG & CA	The informed consent requirements are consistent with the NAG and existing CA regulations.	NA Guidelines 3.2 CA_H&S_Code_125315 Working_Notes_3
(b)	Do not violate the preferences of donors	NAG & SWG	Provision developed to be consistent with an aspirational goal of the NAG. "Donors could be offered the option of agreeing to some forms of hES cell research but not others…The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored."	NA Guidelines 3.6 SWG 12/01/05 Transcript P90.L4
(b)(1)	Cells may be kept for many years	NAG & CA	NAG: "A statement that derived hES cells and/or cell lines might be kept for many years." [3.6(f)] Same standard applies in existing CA regulations.	NA Guidelines 3.6(f) CA_H&S_Code_125315 (c)(4)
(b)(2)	Recontact of donors	NAG	NAG: "If the identities of the donors are retained (even if coded), a statement as to whether donors wish to be contacted in the future to receive information obtained through studies of the cell lines." [3.6(d)]	NA Guidelines 3.6(d) SWG 12/01/05 Transcript P59.L23
(b)(3)	Cells used in future studies	SWG	SWG indicated the need to emphasize all future uses could not be anticipated at time of donation.	SWG 12/01/05 Transcript P83.L9
(b)(4)	May be used in research involving genetic manipulation	NAG	NAG: "A statement that the hES cells and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and nonhuman cells in animal models." [3.6(g)]	NA Guidelines 3.6(g) SWG 12/01/05 Transcript P87.L18 Working_Notes_8
(b)(5)	May be transplanted into humans or animals	NAG	NAG: "A statement that the hES cells and/or cell lines might be used in research involving genetic manipulation of the cells or the mixing of human and nonhuman cells in animal models." [3.6(g)]	NA Guidelines 3.6(g) Working_Notes_8
(b)(6)	No direct medical benefit except autologous	NAG & CA	NAG: "A statement that the research is not intended to provide direct medical benefit to the donor(s) except in the case of autologous donation." [3.6(i)]	NA Guidelines 3.6(i) CA_H&S_Code_125315 (c)(6)
(b)(7)	Donation without any restriction on recipient	NAG	NAG: "A statement that the donation is made without any restriction or direction regarding who may be the recipient of transplants of the cells derived, except in the case of autologous donation." [3.6(b)]	NA Guidelines 3.6(b)
(b)(8)	Consenting or refusing will not affect quality of care	NAG	NAG: "A statement that neither consenting nor refusing to donate embryos for research will affect the quality of any future care provided to potential donors." [3.6(k)]	NA Guidelines 3.6(k)
(b)(9)	Cells may have	NAG	NAG: "Disclosure of the possibility that the results of study of the hES cells	NA Guidelines 3.6(h)

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	commercial potential	& CA	may have commercial potential and a statement that the donor will not receive financial or any other benefits from any future commercial development."	CA_H&S_Code_125315 (c)(5)
(c)	Opportunity to document preferences	NAG & SWG	Consistent with NA principle "The consent process should fully explore whether donors have objections to any specific forms of research to ensure that their wishes are honored."	NA Guidelines 3.6 SWG 01/30/06 Transcript P269.L22
(d)	Additional requirements for donation of oocytes	SWG	SWG identified oocyte donor issues as "complex" and "controversial" requiring special standards.	SWG 12/01/05 Transcript P92.L15
(1)	Description of foreseeable risks	HHS, SWG & CA	Description of risks fundamental to all informed consent; SWG identified specific risks associated with egg donation.	45CFR Part 46 SWG 01/30/06 Transcript P257.L17
(2)	Physician must disclose relationship to researcher	SWG & CA	Consistent with existing regulations that require that "material financial stake or interest, if any, that the investigator or research institution has in the outcome of the medical experiment" to be disclosed.	CA_H&S_Code_24173 (c) (11)
(3)	Informed of option to deliberate	SWG	Requirement intended to remind donors of existing rights. Revised from original requirement based on public comments.	SWG 12/01/05 Transcript P93.L7 SWG_05_03_06_Transcript_P45. WC_029
(4)	Ascertain donor understands essential aspects of research	SWG	SWG agreed in principal to assessment at 12/1/05 meeting. Language revised in response to comments.	SWG 12/01/05 Transcript P118.L11 WC_017
(4)(A-H)	Essential aspects	SWG	SWG identified critical elements from 100009(a)(1-9) that are essential for oocyte donors understand.	
(d)	Statement that embryos will be destroyed	NAG	NAG: "A statement that embryos will be destroyed in the process of deriving hES cells." [3.6(j)]	NA Guidelines 3.6(j)
(e)	Consent from legal parent guardian or	SWG	NAG did not address cord blood and placenta.	SWG 01/30/06 Transcript P260.L10

	progenitor.			
(f)(g)	Cord blood	SWG	ICOC requested that current regulations confirm to existing law and practice where birth mother consents to donation.	ICOC 06/02/2006 Transcript P 101
(h)	For SCNT disclose whether cell available for autologous treatment	SWG	Based on NAG requirement that availability of SCNT cell lines for autologuos treatment be addressed.	NA Guidelines 3.6(i)
S 100110	**Issue**	**Source**	**Comment**	**Reference**
	CA Health Research Fairness Act & Inclusion of Women and Minorities	CA & SWG	SWG identified fairness and inclusion in research as a priority. Provision adopts existing CA policy by reference. Policy mirrors 1993 NIH guidelines.	SWG 08/30/05 Transcript P22.L15 CA H&S Code 100237
S 100120	**Issue**	**Source**	**Comment**	**Reference**
	Record keeping	NAG & CIRM	This section contains general record keeping requirements. Such requirements are also contained in the Grants Administration Policy pursuant to CIRM's general obligations to track use of funds.	NA Guidelines 6.1
S 100130	**Issue**	**Source**	**Comment**	**Reference**
	Materials Sharing	ICOC IP Policy	This section reiterates a core principle of the proposed intellectual property policy. See: http://www.cirm.ca.gov/policies/pdf/IPPNPO.pdf	SWG 01/30/06 Transcript P24.L10