CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE	Summary: CIRM Compliance Program Information Interviews with SCRO Committees and Principal Investigators

The CIRM Compliance Program is designed to evaluate grantee compliance with the Institute's regulations and policies. Program activities involve two discrete steps: (1) an internal administrative review of grantee institutions files and (2) a site visit to perform a review of records and interviews with researchers and staff.

One purpose of the interviews with researchers and staff is to identify policy considerations related to CIRM's MES regulations. Participants are asked to identify regulatory issues that impact the conduct of funded-research. The stated purpose of the interviews is to provide an anonymous summary of comments to CIRM and the Standards Working Group for policy-making purposes.

The following report summarizes interviews conducted between July and November 2008. Some interviewees we asked to clarify comments in writing. Written submissions are identified below.

1.	(a)	Comments related to researcher ability to access hESC lines. Have researchers been able to access appropriate lines for research; have they encountered regulatory barriers regarding access to research materials? General Sense of the Issue: The majority of researchers indicated that hESC procurement did not pose a barrier to research. In many instances, researchers modified their experiments to utilize NIH or HUES lines because these lines have been identified to be acceptable by regulation or SCRO review. Foreign lines posed some difficulty because in some examples SCRO committees had difficulties understanding the consent protocol or process. In one example, (Karolinska Institutet lines) the research provided documentation to enable the committee to make a determination. SCRO committee representatives reinforced the theme that a system for cell line registration (safe list) that identified compliant research materials would improve process efficiency.
	(b)	[Grantee Researcher: SEED]: Availability is an issue for 4 lines so far. Some of the problems relate to distribution from supplier. Non-NIH lines in general take additional time and energy because they require approval. It would be helpful if there were a virtual or distributed bank where acceptable lines could be listed. A list of acceptable line would help improve efficiency. Efficiency / speed of distribution varies between providers. Banks with the capacity to distribute efficiently are important too.

	(c)	[Grantee Researcher: Comprehensive]: There has been some difficulty verifying requirements on foreign lines. The availability of such lines is helpful because collaborators have developed them, so it is desirable to work with materials where the collaborators have a history of working with the materials. Steps have been taken to ensure future procurement is satisfactory to meet CIRM standards.
2.	(a)	Comments related to researcher ability to access oocytes. Have researchers been able to access oocytes? General Sense of the Issue: Oocyte procurement for research has been limited to materials discarded from IVF process. Consequently, research has been limited to small studies. There is also great variability in material collection. Logistically it may also be difficult to procure materials since they often come in later in the day; requiring that experiment start in the evening.
	(b)	[Researcher] The restriction on use of oocytes intended for IVF for which donors have been paid result in the loss of valuable research materials. There are often situations where it does no make sense to create embryos beyond the number required for IVF treatment. It is important to keep in mind that oocytes are critical for developmental biology research not just SCNT or cell line generation. We have been advised that state law also prohibits use of paid oocyted for developmental biology work. This restriction seems counter productive and requires us to discard materials that could otherwise be used in research.
	(c)	[SCRO Chairperson] It is difficult for potential donors to access information. A portal for potential donors with information about research centers would be helpful. It would be helpful to identify mechanisms to link potential donors to research. A WEB-based portal that facilitates oocyte donation might be considered.
3.	(a)	Comments related to oversight of research involving human somatic cells / iPS experiments. The most frequent and extensive comments provide by SCRO committee members concerned the use of human somatic cells. The following three sections identify issues raised. This section identifies questions related to review and oversight of research involving somatic cells. Section 4 addresses comments related payment issues, and Section 5 address comments related to informed consent.

	(b)	[ESCRO Chairperson & Program Director Written Comment] There are 3 categories of possible uses for iPS cells: (1) in vitro only; (2) insertion into non-human animals or developing animal embryos; (3) insertion into humans. At most, category 1 should require ESCRO notification only, and preferably not even notification. The only time that we should have an issue is categories 2 and 3: if the cells are to be inserted into humans or animals. It would be great if CIRM could work together with the Human Stem Cell Research Advisory Committee to distinguish between pluripotent embryonic stem cells and those pluripotent cells that can be derived without the creation or destruction of human embryos (i.e., iPS cells or any adult stem cells that might meet that standard). In the case of the latter, no SCRO/ESCRO review should be required unless the cells are to be introduced into an animal or human. I may be missing something, but I think this would at least remove a significant burden from investigators and review committees, but not eliminate any reviews that might be necessary. Notes: ▸ This comment was circulated to a second ESCRO administrator who concurred with the recommendations of the first commenter. ▸ The recommendation is consistent with the NAS Guidelines 2008 revisions.
4.		Comments related to **payments** for human somatic cells utilized in iPS experiments.
	(a)	[2 SCRO Administrators from Separate Institutions] The CIRM regulations prohibit even modest payments ($25-50) for donation of blood, skin cells, tissue, urine etc. It is generally accepted practice to provide modest payment to donors, and biobanks have stocks of such tissue. Under the current regulations, these tissues are not available for iPS research. The NAS guidelines discuss limitations on payments for gametes and embryos consistent with CIRM policy, but this requirement is not extended to somatic cells and tissue. The NAS acknowledges existing IRB regulations covers this level of procurement. CIRM should allow use of somatic cells and tissues provided. It is important to recognize that the CIRM rules should be compatible with accepted research practice. IRBs have historically determined that such payments are reasonable for donors and do not constitute an undue inducement for participation.

5.		Comments related to **consent** for human somatic cells utilized in iPS experiments.
	(a)	[SCRO Chairperson] For the most part, SCRO/ESCRO committees have to worry about sources of cells and uses of cells. In the case of iPS cells, the source (cell procurement) is really an IRB question. There is nothing special here other than the fact that the cells will be used for stem cell research. To the extent that the genetic material might live on for future uses in research, or clinical application, that is an issue that is not new to IRBs, and historically they have addressed concerns in the consent process.
	(b)	[SCRO Administrator] Cells and tissue are routinely collected through IRB approved protocols. These protocols inform the donor that the cells will be used for research. These banks were developed long before the CIRM rules took effect and the currently do not incorporate the CIRM consent requirements. We cannot use these consented cells for reprogramming work in CIRM-funded studies because it might be considered a cell line derivation. This requirement impedes basic research. For example, one researcher is performing reprogramming experiments in the context of AIDS research. Ideally, the researcher would be able to access cells with varying immunological profiles for reprogramming work. The bank contains consented blood samples from AIDS patients, but due to the consent restrictions described previously, these samples are not available.
	(c)	[SCRO Administrator: Written Comment] We have a project in which the investigator requested to use stored blood to create iPSC from deceased patients who had their blood collected for clinical hematopietic stem cell transplants but unfortunately died before the reinfusion of their cells. The goal of the project is to study programmed immune system regeneration. The requested cells are ethical and scientifically appropriate for stem cell research for the following reasons: • Deceased patients had the disease under study • The research poses no risks to the deceased patients • The use of blood from deceased patients reduces risks to living patient/donors as using blood from deceased patients reduces the need to collect blood for research purposes from living individuals **Regulatory Issues:** - CIRM regulations at 100080, without exception, require the ESCRO to either ensure that informed consent is provided for the use of the cells or ensure that investigators cannot identify the individual source of somatic cells.

		- It is important to maintain links to the deceased patient medical records (with appropriate CA law and HIPAA consideration) in order to understand the medical history when developing the iPSC lines. - HHS Human Subjects Regulations Do Not Apply: Blood from deceased patients does not constitute human subjects research under 45 CFR 46.102(f) [see below for definition] because deceased patients are not living individuals as defined by the regulation. The regulation defining human subjects does not consider whether the blood is linked to identifiable data such as medical records but rather hinges upon whether the individual is "living". Therefore, IRB review is not required and federal rules for informed consent do not apply for research with materials obtained about deceased individuals. - The CIRM regulation places an unprecedented and unwarranted impediment on the research as there are no risks to the deceased patients (they are no longer alive to experience risks) and access to such material (blood and medical records) is not covered by the federal regulations for the protection of human subjects. 45 CFR 46.102(f): *Human subject* means a **living individual** [emphasis added] about whom an investigator (whether professional or student) conducting research obtains (1) Data through intervention or interaction with the individual, or (2) Identifiable private information. It would be helpful if the CIRM rules were consistent with federal regulations for protection of human subjects, in order to facilitate the research, and particularly to assist in national and international collaborations since it appears federal restrictions for stem cell research will change in the next 6 -12 months and many jurisdictions will ensure compliance based on HHS human research rules (at least until specific HHS stem cell rules are promulgated).		