Meeting Minutes
Scientific and Medical Accountability Standards Working Group
August 30, 2005
Grand Hyatt San Francisco
10AM-6PM

Attendance:
Working Group Members

Alta **Charo**
Jose **Cibelli**
Kevin **Eggan**
Ann **Kiessling**
Robert **Klein**
Jeffrey **Kordower**
Sherry **Lansing** (co-chair)
Bernard **Lo** (co-chair)
Kenneth **Olden**
Theodore **Peters**
Francisco **Prieto**
Janet **Rowley** (via phone)
Jeff **Sheehy**
Jonathan **Shestack**
Robert **Taylor**
James **Willerson**

CIRM
Zach Hall, Ph.D., CIRM President
James Harrison, CIRM Counsel
Geoff Lomax, DrPH. Senior Officer for the Standards Working Group
Kate Shreve, CIRM staff
Nicole Pagano, CIRM staff
Jennifer Rosaia, CIRM staff

[Welcome, Sherry Lansing]

[Working Group Introductions-SWG Members]

[Roll call]

Agenda Item #4: Approval of Minutes from July 6th 2005

Corrections requested:

- Page 7, paragraph 5: change “closing” to “cloning”
- Page 13. next to last sentence on the page: change “Key issues faced by **Kiessling** et.al. and the Ethics Board developing the first IVF lab in Oregon” to “Key issues faced by **Kiessling** et.al. and the Ethics Board developing the first egg donor program for stem cell research.”

Motion: To approve minutes from July 6, 2005 meeting with corrections
Motion: Lansing
Second: Prieto
Motion passes unanimously

Agenda Item #5: CIRM Staff Report

Geoff Lomax provided a staff progress report outlining the following:

- Amended timeline for draft regulations including the drafting period and APA rulemaking process
    - Layered mechanisms (including public sessions and the opportunity for web-based public comment) for gathering public input during the drafting as well as APA phase of developing final CIRM regulations
- The proposed format and content is designed to focus the discussion in the public sessions—the content has been distilled from the work product of the study groups. The sample questions provided are not intended to be proscriptive or inhibit other questions from being raised but rather to stimulate discussion.
- Process the study groups used to arrive at proposed questions-there was variation across study groups with regard to the level of staff involvement in drafting the questions.

Olden: The Working Group should propose an "explicit" policy with respect to access to the benefits of SC research. Support for SC research has rested on the promise of access to all—the NA Guidelines raised the issue of diversity with respect to donor recruitment but not with respect to access. Both need to be addressed.

Charo: Questions a) whether it is appropriate to include references to stem cell sources other than husks in the framework for the public session and b) given the common confusion regarding what falls under "preclinical research" which covers the use of cell lines in lab or animal testing, argues that items under the informed consent category would be more appropriate for the donor recruitment section.

Kiessling: Expressed concerns that these discussion points for the public session may be misinterpreted by the public as representing the priorities of Working Group members.

[Hall clarified that these questions represent the distillation of ideas that came from the discussion of the study group members and were not generated but organized by staff and that it was up to the Working Group to decide whether the format was a useful one to frame the public sessions.]

Klein: This process facilitates a systematic approach to collecting information so that we can more effectively focus, sort, and compare [feedback received].

Lansing: This intent can be effectively communicated to the public before the public sessions.

Prieto: In agreement with **Charo** that informed consent issues belong under donor recruitment. Research on non-embryonic stem cell lines should also be addressed given that Prop 71 permits funding for sources beyond hESC research.

Hall: It is expected that the final regulatory document will include a statement addressing the use of adult stem cells—it is not inappropriate to get public feedback on non-embryonic SC research in the upcoming public sessions.

Charo: Not inappropriate but the topic comes out of nowhere. [Reference to adult sources] needs to be more clear/contextualized.

Olden: Recommends holding public sessions in the evening so working members of the public will be more likely/encouraged to attend.

[Public comment]

Reed: Even among highly educated people, there is confusion [about the need for this research] particularly given some of the scientific tools that are alarming to the lay public (such as chimera or animal/human mixes. If statements could be added that illustrate the need for this research it would be helpful to those who do not have your expertise.

Lansing: This will be taken into account [by staff]—it will help our communication to the public.

Motion: To approve format and questions for Standards Working Group/CIRM public sessions as amended by Alta Charo
Motion: Prieto
Second:
Motion left on the floor-not voted on.

Agenda Item #5: Consideration of Standards Working Group Bylaws

James **Harrison**, counsel to the CIRM, framed the discussion on the SWG Bylaws.
Purpose: These are the guidelines and procedures for the operation of the Working Group. These represent the mission of the Working Group based on the framework established by Proposition 71, including composition, appointment of co-chairs, conflict of interest requirements, meeting procedures and governance of meetings.

Sheehy: Ambiguity remains in the language (see 3(b)) as to whether access issues will be addressed by [the SWG]. Should this be more directly stipulated in [the SWG] bylaws?

Klein: Should these be in the bylaws or adopted as resolution by this committee to be within its jurisdiction?

Sheehy: Either way, [a commitment to address access issues] should be formally stated by this committee.

Hall: The primary charge of this committee is to set the guidelines that will govern the research [funded by the CIRM]—the question of access is complicated one, politically, ethically and goes beyond the governance of the research itself to how it is brought to the clinic. This is an important issue for the ICOC to address as a whole. A strong statement [about making this research broadly accessible] from this committee would be very valuable. The difficult part will be to say exactly what should be done to make that happen. This could consume this group and has have IP, political, Prop 71, and financial implications.

Sheehy: This would not be the place where we would end up with regulatory language but could be included in our charge so that whatever does end up being produced [which will likely be by a separate entity] makes its way though this working group. Given that there are ethicists [on the Standards Working Group] we can make a broad policy statement or resolution but that doesn't have the same effect as having this Working Group have an advisory role on IP or access issues proceeding to the ICOC.

Prieto: Under 3(a) and 3(b) [see Bylaws document] these issues are under the charge of this committee, it is almost expected that we'll make recommendations to the ICOC. This will touch upon IP and other issues that will come before the ICOC. I don't know if the bylaws are the appropriate place for this but we need to put our opinions out there with regard to access to therapies when and if they become available.

Taylor: Agreed. Article 3(b) is an open opportunity to insert a guiding principle that access and diversity be part of things we discuss. Else there is nothing specific about the other language in this article—it is important to let people know this is a priority [of the SWG].

Lo: To clarify, there are several related issues emerging in this discussion. 1) we want to make it clear that providing input to the ICOC on issues related to access and diversity is part of the charge of this working group recognizing that there is a lot of other pertinent expertise on this [available to the ICOC] but that this working group should be part of the discussion; 2) that a substantive statement on equal access should be addressed in our bylaws [which, to me, are actually procedural rules to guide the SWG's meetings, etc.,] The question is whether this statement belongs in the bylaws.

Prieto: Under Purpose, Article 2?

Klein: The ethical issues of access are fundamental. We should be making a statement. There are two issues of diversity that need to be addressed separately: one is with respect access to therapies and the other with respect to diversity of biological materials. Is there a motion to pass these bylaws with a direction to Jeff and others to draw up language [to address access and diversity].

Sheehy: Good suggestion.

Lansing: Second.

Kiessling: As a reminder, we have learned the hard way about the consequences of separating the fundamental research from the question of diversity and access and the fact that all populations must be included in the design of research protocols in order to ensure that all people are going to have access and benefit from the research. NIH now requires you to justify any exclusions from study groups—e.g., if you are conducting an adult study, you must justify why children are not included. This working group must have the concept of total access at the end of research be a part of its thinking at every stage.

Dr. Hall: Maybe Francisco would join that effort.

Prieto: Yes.

Motion: **Klein**
Second: **Lansing**

[Public comment]

Reed: While access and diversity are important goals, there is a danger of being too proscriptive. I would hate to see anything which requires people to prove this [research] is going to benefit everyone before the research could go out. This should be a general charge rather than specific recommendations.

Lo response: We are saying that we want these topics to be part of our discussion-we are not saying anything about specific recommendations.

Reynolds: I've been concerned about an apparent shift in the tone that characterized the campaign which was "trust us with your money, and we'll do our best to get therapies and cures to all Californians." But recently, there seems to be more emphasis on "our job is to do the research and fund the science and from there it is out of our hands." This discussion is critical to that distinction. In Proposition 71, under the statutory charge of this working group it says the responsibilities are to recommend to the ICOC standards for all medical socioeconomic, and financial aspects of clinical trials and therapy *delivery* to patients. The bylaws say *therapy development.* There is an important distinction between these two words. The statutory language has precedence over the bylaws, but I encourage you in your bylaws and intention to keep [the issue of access and diversity] in mind from informed consent for gamete donors to accessibility for patients.

Lo: In 3(b) you would say therapy delivery instead of therapy development?

Reynolds: I would say both.

Klein: I would accept a friendly amendment to include both words.
Lansing: Seconded.

Harrison: You may want to adopt one modification to Robert's Rules of order to permit friendly amendments to be accepted without having to take a vote of the working group.

[**Klein** proposes an amendment to adopt this suggested modification in the bylaws].

Lansing: Second?

Motion: To approve the bylaws with the provisions that we charge Jeff and Dr. Olden and any other committee members that the Chairs so designate to bring back additional supplemental language to include with recommendations on the part of the bylaws we included as well as addressing both access and diversity specifically.

Motion: Klein
Second: Lansing
Amendment 1: To change language to include in 3(b) the use of the language therapy development and therapy delivery
Amendment 2: To adopt amendment to permit friendly amendment to be accepted without taking a vote of the working group.
Motion passes unanimously.

Follow-up: The current amended language in the bylaws reads:

ARTICLE II. Purpose.

*The SWG is created for the purpose of recommending scientific, medical, and ethical standards to the ICOC. This purpose will be accomplished by: (1) recommending standards for all medical, socioeconomic, **diversity**, and financial aspects of clinical trials and **therapy development and delivery** to patients, including equitable access to therapies; (2) recommending standards for the oversight of funded research; and (3) advising the ICOC on relevant ethical and regulatory issues.*

ARTICLE III. Functions.

*The duties of the SWG s**Hall** include the following:*

(A) *Recommend to the ICOC scientific, medical and ethical standards;*

(B) *Recommend to the ICOC **standards for all medical, socioeconomic, diversity, and financial aspects of clinical trials and therapy development and delivery to patients, including among others, standards for equitable access to therapies and safe and ethical procedures for obtaining materials and cells for research and clinical efforts for the appropriate treatment of human subjects** in medical research consistent with paragraph (2) of subdivision (b) of Section 125290.35, and to ensure compliance with patient privacy laws.*

ARTICLE VI. SWG Procedure for Recommending Scientific, Medical, and Ethical Standards.

Section 2 (Voting Procedures).

Amendments to pending motions may be made with the concurrence of the maker of the motion and the second, unless a member of the ICOC requests a vote on the proposed amendment, in which case, action on the proposed amendment sHall be taken by a majority vote of a quorum, before the vote on the pending motion.

Agenda Item #6: CIRM Interim Guidelines

[Lo provides preamble re: the importance of passing interim regulations and the process for developing final regulations including opportunity for public comment during the preliminary drafting period as well as the formal APA rulemaking period. This working group will have considerable opportunity to draft the final regulations which may include addressing topics that are not covered in the NAS Guidelines on which the CIRM Interim Regulations are based such as cell lines derived with non-CIRM funding and work with cell lines derived before the effective date of the regulations as well as resolving areas of inconsistency or lack of clarity. Approving these interim guidelines does not preclude making substantive changes in the draft final regulations.]

Hall: Interim guidelines are needed to approve the 1st round of training grants. We will need the interim guidelines to cover anything that might be done under those grants
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[Hall provides context for the proposed interim guidelines-that they represent the NAS Guidelines adapted into regulatory language consistent with CA State law with an additional clause that allows for the establishment of joint ESCROs]

[Geoff Lomax details the changes made to adapt the NAS Guidelines into appropriate language for the CIRM]

Dr. Taylor identified and inconsistency re: permissible length of time a blastocyst may be cultured in vitro in the proposed interim guidelines with respect to Section 100008(e).

Action: The range of 8-12 days on p.6 section 100008(e) will be changed to 12 days to maintain consistency within the document and with Prop 71.

Lo: If funding is given under these draft guidelines [e.g., training grants] and then changes are made to the guidelines, what guidelines will the grantees be required to follow? This is not an uncommon event [in institutional policy development].

Hall: The grants policy will provide that they will be required to follow the interim guidelines until they are superseded by the final guidelines. [Should changes be made to the regulations] a notice would be sent out to all CIRM grantees.

Klein: This would mean that investigators who had done work under the original set of guidelines would not have to redo their work?

Hall: Yes.E.g., if you derive lines under the interim guidelines and we change the guidelines, you would not have to throw out the lines. These lines would be grandfathered.

Harrison: The following clarifying changes are also requested:

1) Change from "and" to "or" in Section 00(a)-to read "the Chapter covers all research funded by the CIRM that involved the derivation of human embryonic cell lines or the use to hES cell lines derived from…"
2) Deletion of section 00(a), subparagraph (b)3 . This language is unnecessary and stated more effectively in section 02 which addressed the issue of previously derived cell lines.

Kiessling: Does this committee feel it would be appropriate to add a 00000 (a) that deals with blastocysts derived from parthenogenetically activated eggs because all of these guidelines should apply to that. Else [this area] of research remains unaddressed.

Hall: We can expect that it will be possible to be able to derive lines in ways other than those outlined here—we could draft general language that would apply regardless of how a cell line was derived.

Cibelli: What was the scope envisioned by the National Academies?

Charo: Human embryonic stem cell research dealing only with blastocysts from fertilization or NT. There was a deliberate decision to narrow the scope to cover the bulk of research that is [currently] going on in this country. As a result, there are omissions in the scope of work [covered by the NA Guidelines].

Kiessling: It is important that we make it clear when eggs are involved because that distinction represents a huge issues to a large percentage of the population in our country compared to other types of technologies. [**Eggan**'s] work should not be lumped into these categories that are using human eggs for their work. It comes down to the definition of "embryonic."

Hall: There would be universal prohibitions [e.g., putting certain lines into other organisms] that would apply regardless of derivation source—so the egg donor issues may be gone in this case but other prohibitions should apply.

[Interruption in proceedings]

Willerson: Could you add the phrase "or from any other source?" in Section 08(a).

Klein: Willerson's approach is appropriate. –in order to fund research like [**Eggan**'s] we need to have standards in place.

Eggan request for clarification as to where amended language would go, section 08(a) or 00(a) 4.

Harrison: It could go in both locations as well as in the first section that defines the scope of the chapter. [In response to clarification requested by **Prieto**] In section 00 I would suggest adding this language as a new subparagraph 4 in subdivision A using the language "any other procedure."

[Further discussion on the placement of draft language. Final language suggested "from any other source or any other procedure" to be added to section 00(a) as a new subparagraph 4 with a corresponding change in section 08(a)]

[Discussion of Alta Charo's suggested changes proposed in an email dated 7-05-05—resolution that more extensive changes will be deferred to a later date-post adoption of interim guidelines]

3) **Motion: To approve changes to the proposed interim guidelines**

a) Change from "and" to "or" in Section 00(a)-to read "the Chapter covers all research funded by the CIRM that involved the derivations of human embryonic cell lines or the use to hES cell lines derived from…"
b) Deletion of section 00(a), subparagraph (b)3 . This language is unnecessary and stated more effectively in section 02 which addressed the issue of previously derived cell lines.
c) final language suggested "from any other source or any other procedure" to be added to section 00(a) as a new subparagraph 4 with a corresponding change in section 08(a)]

Motion (call to question): unclear
Seconded: Klein
Motion passes unanimously.

Charo: Should sections 00 and 02 that address the grandfathering of cell lines be more explicitly stated? The guidance needs to be explicitly clear with respect to covering lines that are derived in the near and distant future. [Researchers] need to know that NIH-authorized lines have already received their IRB review, that there is already documentation of informed consent that they do not have to recreate that documentation. When in comes to in vitro experiments they would have to follow the CIRM guidelines, but wouldn't it make sense to say that documentation for the NIH lines is presumed? This issue has dogged [the research community]

Hall: It's not only the NIH derived lines-others may come available in x months.

Charo: I was not suggesting deleting this section but rather adding specific language [to the section that addresses grandfathering] –that NIH and HFEA [derived lines would be

grandfathered-given the screening process cell lines are required to go through to be HFEA and NIH approved lines] so that investigators would not have to recreate the documentation to determine that the cells were “ethically derived” .

Eggan: This may be broadened to a number of other [sources]

Rowley: It’s important to clarify that the NIH has not derived any cell lines. They all come from different institutions. They are NIH *approved.*

Specific language for section 00 and 02 suggested by Alta **Charo**:
add a subparagraph that reads “lines approved for NIH or HFEA funding will be accepted as having already complied with documentation requirements concerning compliance with informed consent and Institutional Review Board oversight.”

Eggan: Would add “or deposited in one of the following accepted tissue banks” including, for instance, the UK Stem Cell Bank or other banks which this body can agree passes those litmus tests.

Charo: We need to wait until we can determine what criteria to apply to these other sources.

Eggan: Strongly agree.

Hall: Not clear what the practice will be for cells deposited in the UK Stem Cell Bank.—we should seek agreement on basic language [as suggested by Alta] and consider other sources on a case by case basis. Else we could consider source with “equivalent standards.”

Klein: Setting such a benchmark would save a lot of unnecessary documentation

Lo: There is some ambiguity on the NIH website regarding the type of consent required of the gamete donor [for NIH-approved lines]. On the one hand, there is the principle of grandfathering in [cell lines] that have been approved and have been w ell characterized; on the other hand, there is the questions of what standards were in place at the time [the cell lines] were derived. We may include a “warning” as we consider guidelines that have been deemed appropriate by other bodies [such as the NIH] so we understand what kind of standards were applied to the review and approval process—so the equivalent standards sounds appropriate.

Hall: Do you think it would be a mistake to say that all NIH lines are eligible [for CIRM funding]?

Lo: Need further thought. On the one hand we can say we use them because they are approved and well-characterized and would be useful for some types of research but would not be likely to be used for transplantation for a variety of scientific reasons. There is a clear lack of clarity regarding the standards by which the NIH lines were approved.

Hall: Is this a serious enough issue that you would advise not automatically qualifying NIH lines?

Lo: We came down on the side of approving NIH guidelines because the work that was being proposed in that case was purely viable laboratory and non-human/animal research.

Hall: You raise the issue [only] as a concern
Lo: Correct.

Kordower: You mean [the NIH lines are not likely to be used in clinical transplantation, but they will be used in preclinical studies?

Lo: Absolutely. The issue comes up if a gamete donor whose materials were used in the derivation of NIH lines did not wish to have his/her materials used for human transplantation.

Hall: In the cases that you looked at, your judgment was that [your concerns] were not serious enough to disqualify those lines.

Klein: There is a proposal on the table for modified language including an equivalency using the stem cell bank in England as a benchmark and including language that would permit additional stem cell banks if they met an equivalency standard of that kind of gold standards as is required by the UK stem cell bank?

Eggan: Do we want to actually review each one of those banks before we allow them in or [should we consider] whether or not we wish to make a large blanket statement

Kiessling: How much trouble is this going to save the investigator? Is this simply a matter of ordering a line from the NIH who will provide you with all of the necessary documentation or will this mean re-qualifying a line?

Eggan: This is saying that [the CIRM] wouldn't need the documentation because it has already been demonstrated that these are well-documented cell lines. It would be more akin to ordering something from the ATCC rather than having the generate a huge dossier-which is a substantial advantage to a scientist. I feel comfortable with the level of review which seems to be going on at the UK Stem Cell. However, I have some concern given that it is one thing to say that other people are adhering to equivalent standards, it is another thing to [ensure that they] actually do it.

Kiessling: Does the NIH provide you with all of the documentation you need when you order a cell line?

Lo: You do are not sent the documentation itself-[getting documentation would present a lot of difficulty for the investigator]. The NIH website [that has now been removed] described the process under which NIH-approved lines were reviewed and approved. [Investigators] would have to trust that the NIH approval of lines was based on careful review of those documents.

I have been told that it would be quite time-consuming for investigators to actually provide that documentation to their IRB. So if we felt comfortable enough that the right materials were reviewed in a thoughtful manner, that review need not be repeated by each individual local IRB.

Charo: We know the NIH standards for determining lines to be approved for funding. We also know a lot about what the standards were in the UK under UK law and HFEA policy for what cells they would allow into their bank. This information was summarized and distributed with the NAS report. The key elements that correspond to the CIRM requirements under Prop 71 include the noncommercial aspect of the material collection and the voluntary informed consent aspect of the collection. To the expect that Prop 71 sets bare minimum standards—those two collections meet those standards. The Study Group dealing with interstate and international collaborations has begun to outline how to identify other lines or other institutions or other state and national laws and determine whether or not they do or do not meet not only Prop 71's bare minimum standards but standards identified by [the SWG] as being nonnegotiable. We haven't gotten to that discussion so we don't know how to amend the regs beyond [including NIH/UK Stem Cell Bank approved lines]

Eggan: I would move to include those.

Hall: If we put the phrase "equivalent standards" or its equivalent such as "appropriate standards" it would become the responsibility of the ESCRO at the individual institutions to establish the ethical provenance of lines and make a decision on a case by case basis particularly in the context of international collaborations. As Bernie's case illustrates, this is already being done at many institutions—this will not give them a new and unexpected responsibility. But if we merely state the minimum, it doesn't close the door to using outside lines but puts the burden of proof on local institutions to show they're of an equivalent standard.

Prieto: It would be best to keep this a fairly general statement. [In agreement with **Hall**] Would we amend the current language?

Hall: The problem with the language as it is is that there is not provision for cell lines that may be announced tomorrow. The intent is to set a general standard and place the burden on the individual institutions through their ESCRO committees to demonstrate that whatever lines are being use by their investigators with CIRM funding are compatible with these standards.
I would suggest the wording be as Alta suggested, as amended by Kevin, and would add "or equivalent standard".

Taylor: I am concerned that the levels of standards that we are talking about might not be the level we want to achieve at the CIRM. I don't believe the UK Stem Cell Bank has the gamete donor issues discussed that [Bernie **Lo**] raised in his concern about the NIH baseline. I am concerned that we will be watering down the standards we really want to promulgate.

I accept that grandfathering is important but am concerned that we are adopting language that will have the effect of lowering out standards.

Rowley:[was involved in writing the NAS Guidelines on Banking] I am certain that the UK Stem Cell Bank required that the gamete donors gave informed consent for the cell lines accepted into the UK Bank.

Klein [addressing James Harrison]: If we have an equivalency standards in our guidelines which go through the Administrative Procedure Act, then, whether it's an ESCRO committee or the SWG, there could be a judgment about equivalency. If we don't put an equivalency standards in, then we are not going to be in a position to approve grants. This will give us future flexibility when other stem cell banks become well-established and their procedures are known or as the international society develops standards that are well-known.

Harrison: Correct. If the research involved cell lines that aren't covered by this exception, you would need to go through a formal process in order to amend the regulations to create a new exception.

Klein: So my suggestion would be that equivalent standards is important—where you house that approval has yet to be decided.
The other point regarding preexisting lines is that there needs to be a provision for a waiver procedure.

[Discussion repeated for the benefit of Dr. Hall who had been called out of the room]

Hall: I think it will be a long-term problem for the CIRM to deal with this issue. If an investigator anywhere in the world comes up with a new cell line, it will present the questions: can the line be used by the CIRM investigator? Who makes the decision of whether it can be used? Will the CIRM certify new lines for use by CIRM investigators or will they be certified elsewhere?

Cibelli: The UK Stem Cell Bank has a Steering Committee that reviews documentation before they accept a cell lines based on strict criteria on which, including documentation of informed consent and peer review for the work of deriving cell lines—this is something we will have to do in the future as the CIRM ethics committee. I would like to echo Kevin **Eggan**'s comments that before we say something along the lines of adopting someone else's guidelines, I would rather say we will make sure that the cell lines when they are submitted to our bank will [meet] this criteria. If we don't have the criteria today, that's fine. We need to know.

Lo: These are issues that we will need to address. The question is what should we put in place as interim guidelines that will serve for the next nine months and how detailed should they be?

Eggan: The important thing that Bob raised was that just by saying that we allow this equivalency statement doesn't mean that we cede the authority to judge equivalency.

Lo: Who judges what is equivalent?

Eggan: It could be up to both us and the ESCROs to judge equivalency.

Hall: It says, as a practical matter, that we should let the ESCRO committee decide this.

Eggan: We may want to act like the Supreme Court of ESCROs, and essentially almost all decision is based in a way on case law. We could make a general statement throughout all of California about a certain cell line to illustrate why a certain cell line was incorrect.

Hall: We may ultimately want to do that, either at the level of this committee or through developing a statewide committee. At this point, having this committee act in that capacity is probably incorrect. We should tie compliance with standards to funding—we're going to give you the money, here are the standards we expect, it's up to you to show us that what you're doing meets these standards or their equivalent. So we don't cede our authority to say what the standards are or that you haven't met the standards. It relieves us of the working burden of proof.

Klein: To maintain our flexibility it would be equivalency as determined by he ESCRO or set up by this committee.

Hall: For the interim, if we just say it requires us to do that-- I suggest it will require a longer discussion about how that will be done.

Lo: Is this a place where there could be some ambiguity in the interim regulations as opposed to being too specific now on an issue that may not come up?

Klein: You could establish flexibility in the regulations by saying, "equivalency as determined by the ESCRO committee or the SWG or a group set up by the SWG" which would cover multiple approach and avoid having to proposed revisions through the APA.

Hall: I would argue to leave it to the ESCRO committee in the interim regulations [which will be in effect for 270 days] and have a discussion at a later date about the right way to do it—maybe the document we present on November 1 would offer either one or all of these three alternatives.

Lo: The following issues are at play here:

1) what lines are we going to accept 'right off the bat'
    a. The proposal was the HFEA or UK Stem Cell Bank
2) Equivalent standards
    a. Do we want to put a provision for equivalent standards?
    b. Should the ESCRO determine this for the next nine months or
    c. Should this be determined by the SWG/CIRM, ESCRO, or a group set up by the SWG.

    These are independent choices that should be addressed independently.

- **Charo** [responding to an earlier request for clarification on the UK Standards] : The [UK] standards are embodied in the application that you file to deposit cell lines with the UK Stem Cell Bank.
- Like the NIH it does not explicitly require consent from [gamete donors providing gametes for IVF purposes] So there will be uncertainty.
- They do have extensive and detailed questions about other aspects of the consenting process and some rules that go beyond ours with respect to donor control of use of cell lines
- The UK Stem Cell Bank will automatically accept anything on the NIH-approved list [so there is a snake swallowing its tail phenomenon]

Unless this group wants to take a position about the need for consent from anonymous sperm donor [retrospectively] [one of the controversial and somewhat tangential NAS recommendations]—except for that it would seem there would be little problem in taking the NIH and UK Stem Cell Bank lines, grandfathering them in terms of documentation requirements and then leaving the discussion of equivalency separate as we discuss this list beyond these two sources.

Kiessling: The consent doesn't just apply to sperm donors-it also applies to anonymous egg donors.

Charo: Right. I'm using the most typical example—anonymous sperm donors are more common (~10% of frozen embryos)

Cibelli: In agreement that we need to move on a keep things general. Leaving this to the local or regional ESCROs may be problematic because we do not know how these bodies will operate. There may be different standards across institutions with respect to approval of cell lines. At some point as this committee, we need to have standards.

Hall: One of the roles that the CIRM can play is in coordinating the activities of the ESCRO committees to be sure that they are equivalent cell lines—it is everyone's interest to have common best practices, interpretations, and standards. While there is some danger [of significant variation] there is little. Institutions, given the sensitivity of the subject, are going to take their ESCRO responsibilities very seriously. To refer in the interim to the ESCROs is the best solution.

Cibelli: To clarify--we are talking about funding, not banking.

Hall: We can only pronounce on what we fund. However, we need to deal with the issue of institutions housing CIRM-funded and non-CIRM funded research and ensure that dramatically different standards applied to CIRM-funded compared to non-CIRM funded research.
Institutions have a strong investment in doing this right-we can say what we expect and expect that they will match that. We have a big stick in the end which is our funding.

Lo: Let's first try to resolve whether to grandfather NIH, HFEA, and UK Stem Cell lines. Then we will address equivalent standards.

Eggan: We should grandfather those lines in—if we don't, nothing is going to get done by the scientists for another 9 months anyway. It takes so long to gather those documents and send them to the ESCROs that if we don't take Alta's advice, it's not going to matter. We should leave the other issues for later.

Kiessling: The basic question is for most of the stem cell lines already banked, consent by anonymous donors is problematic because even if they consented to have their material used for research purposes, the consent wasn't necessarily for stem cell research. The charge of this committee is to decide whether we are willing to allow CIRM funding for cell lines that are deposited that have been approved by both the NIH and UK licensing board from people who did not consent to have their gametes used for SCR. This would be a small percentage of lines but we would have to accept that we would be grandfathering in some ambiguity for the anonymous donor with respect to knowing the outcome of their donation to research?

Kordower: Are there items that they have excluded-have they said you can't use [the materials] for

Kiessling: Most infertility clinics have in place [consent language that includes] the possibility that embryos not used for family building may be donated for research. Almost no consent form created prior to 3 years ago addresses SCR. This is a gray area. I think it's a fairly small percentage of lines that have been derived from anonymous donors. Lines derived from couples have gone back to the couple in the consenting process. If we are comfortable with this ambiguity for this small percentage of these lines that came from anonymous donors that did not give consent-then we are OK.

Lo: The NIH process is a public governmental process. I think there was a policy decision made at NIH and by the Administration to allow those lines to be used for research. There is some precedent for saying that in light of this ambiguity, given that the lines were derived at a historical point in time, that the process was deemed acceptable by the federal government.

Eggan: Has the HFEA taken up this question?

Charo: The application to deposit cell lines in to the UK Stem Cell Bank is basically an application that says did you derive these under an HFEA license? If not, can you prove that you met equivalent standards to HFEA? Everyone is playing the equivalency game. In their set of question re: equivalency, they omitted any question about obtaining consent from anonymous donors which suggests that they did not see it as a crucial element in making the derivation process ethically equivalent to the one that is used in the UK. The UK has had anonymous donation of gametes up since 2003, so the embryo supply they would have been working with locally for their own derivations would have included anonymous donors. Since 2004, they have instituted a recordkeeping practice that allows

people to go back to the donors in a reproductive context with all sorts of protections—but it means that they could change their policy, but only prospectively. This is the approach the NAS was coming from as well.

[Unclear dialogue-please see transcript pages 97-98]

Willerson: We could grandfather those cell lines that were approved for human research or cell-based research where [approval] was specifically provided or where SCR or cell-based research was not specifically excluded. We should grandfather these cells.

Charo: The UK will not permit the deposit of any lines in which the donors have any control over the subsequent nature of the research. So there couldn't have been any exclusions attached to any of those lines

Willerson: We could be specific about that.

Klein: Are the Harvard lines in the UK SC Bank?

Eggan: The Melton lines are in the process [of being deposited] or have already been deposited in the UK SC Bank.

Klein: Motion to approve grandfathering of the NIG lines and lines deposited in the [UK] Stem Cell Bank.

Olden: Second

[Public comment]

Steve Peckman [UCLA]- Confused about what is being proposed will be grandfathered in and how this will be done. If the proposal is to identify certain cells in certain banks for which is would be unnecessary to provide full documentation of provenance to an IRB or ESCRO, this would be appropriate. However, the question of an equivalency statement is a diversion from this discrete proposal. Request to focus motion on the topic of what documentation an investigator who wants to use lines from a specific bank would be required to provide [an ESCRO or IRB]

Klein: The motion is specifically that the NIH lines and the lines approved by UK Stem Cell Bank would be exempted from the documentation requirement. There will be a separate discussion of equivalency.

Reed: Does this pose a legal threat?

Peckman: Reminder that the NIH approved lines already meet a criteria set out in August 2001 which require that there be consent for research for the use of those cells.

Charo: The NIH required consent from the "owners" of the embryos. In many cases, that was a couple, there might be an anonymous donor who was not consented. The NIH did not require that background third party to be contacted. It's not that the documentation is lacking—there is genuine uncertainty. We do not know whether NIH approved lines involved an anonymous gamete donor.

Peckman: We are in the territory which is equivalent to any stored tissue that's in a refrigerator or repository or bank where a patient has had tissue extracted that may be used for future research. It's hard for me to differentiate between the two.

Reed: Can we say insofar as legal precedent has been established that the US has determined that these may be used for research that we may do so?

Klein: We're creating a process that would go through the APA to be adopted [as law] By exemption these lines from documentation, we would avoid legal contest over that documentation.

Motion: Motion to approve grandfathering of the NIH lines and lines deposited in the [UK] Stem Cell Bank.
Second: Olden
Motion passes unanimously.

[Break for lunch]

Lo: Two goals for the afternoon session:

1) gain closure on interim guidelines to make a recommendation to the ICOC
    a. This will not involve resolving larger issues which will be addressed in the drafting period of developing final guidelines
2) Flag key issues to return to at a later date in order to draw up final regulations

Do we add a provision [to what has already been voted on] that set equivalency standards?

Hall: This is a difficult issue we will face over the long term. It will be hard to set tightly proscribed standards that are the only standards that we accept-- At the same time we need to set minimum standards. What amount of variation [in standards] we will accept will be a difficult job to figure out. We have the remaining issues to address of :

1) cell lines that were derived before the NAS standards
2) cell lines that were derived up until these standards get accepted as permanent regulations

The issue is how to give scientists as much latitude as possible to work with highly desirable cell lines that are being developed without violating our own ethical standards.

Shestack: Are there a large number of cell lines from around the world that will ultimately be made available to CIRM scientists?

Hall: Some of the recently developed cell lines are already being used by US researchers. I'm sure CA investigators will want to use them as well.

Shestack: Where were these lines developed?

Hall: Preeminently S. Korea. Specifics are unknown. S. Korean lines are the focus given their expertise with SCNT. These are being made available to US investigators [mechanism of purchase/distribution is not known]

Kordower: Pittsburg collaborators.

[Other: Israel, Australia, Sweden, UK]

Eggan: We're trying to establish a cooperative agreement with [the S. Koreans] to get their lines.

Shestack: [Before we consider this issue] we should determine how much cooperation is already going on.

Eggan: More and more groups are beginning to or continue to derive new lines-e.g., the group in Chicago under Herlinsky has derived a number of new lines that would be desirable.

Klein: The International Stem Cell Forum is looking at characterizing ~75 lines that are thought to be of a high standard—they are trying to qualify ~75 lines under their standards and protocols.

Hall: Does that include the S. Korean lines.

Eggan: No.

Klein: Korea is on the list to become part of the International Forum.

Taylor: Concern for creating a two-tiered classes of cell lines. Are we painting ourselves into a corner grandfathering in cell lines that may be useful preclinically but not therapeutically?

Hall: These guidelines will only apply for the next 9 months.

Taylor: If we are grandfathering cell lines, these guidelines will affect the CIRM beyond 9 months.

Hall: It is unlikely that we'll have clinical trials coming through before these [regs] are completed. If someone puts in a grant for a clinical trial, the cell lines used will have to meet the new standards.

Shestack: The question is do you want to get the work done now? There is a lot of discovery before there are therapeutics. If you do that you will ultimately have two sets of standards. CIRM-derived and everyone else's. Does this create a problem—it's the only way to get that work done. It will be a while before you have good cell lines production here.

Charo: [Addressing **Taylor**] We are going to run into this dilemma regardless what we do. Even if you have perfect tracking information, how you manage cells in your lab is not likely to meet GMP standards that the FDA requires when you take tissue for therapeutic transplantation if all you are doing is lab work. In many cases, perfectly identified lines still would end up not being usable for therapeutic transplantation.
Maybe we should focus on ensuring that all cell lines are clinically suitable for transplantation—don't know if we'll ever get there unless every basic science experiment is done at a GMP facility.

Lansing: Unless there is something egregious in the [proposed] interim guidelines, I think we should adopt them--they are allowing us to announce training grants. We'll be lucky if we can give out grants and start any real experimentation.
We can attack major and minor problems with the guidelines subsequently.

Klein: The NIH lines are not clinically useful but we need to have them included in out studies because they comprise so much of the existing body of work. I propose to make a motion that cell lines that meet an equivalent standard to the UK SC Bank and other identified benchmark organization this committee may designate [e.g., the International Stem Cell Forum] would qualify under this section of the waiver of documentation. This is relevant during the next 9 months because this language is broad enough to allow us to consider those 75 lines that the International Stem Cell Forum is designating at a later standards meeting.

Hall: Is there a way we can provide some mechanism that would allow those lines to be used if they met a certain standard?

Klein: They can be used—we're determining whether they need documentation.

Eggan: They could be used but they would have to go through a more careful ESCRO review. They are not automatically grandfathered in at this time.

Lo: This is about waiving the requirement for documentation that ESCROs would otherwise have to have [for NIH/HFEA lines]

[Discussion of crafting appropriate language to approve equivalency in concept]

Klein: The motion is to modify section 02—cell lines that are developed under standards equivalent to the UK Stem Cell Bank and other benchmark organizational standards if later approved by the SWG as an equivalent, would qualify for the waiver from documentation.

Charo: Clarification—the HFEA does not license stem cell lines-it licenses centers and approves research protocols. You are referring to two separate things 1) lines that have been deposited in the UK SC Bank which have met the Bank's criteria; 2) lines that have been approved for use by a HFEA licensee because these may be using non stem cell bank lines. (but would qualify for the waiver because of the review process they have gone through at part of the licensing process.) So we are dealing with lines from 3 entities:

1) NIH
2) HFEA licensees
3) UK Stem Cell Bank

Klein: This language falls short of providing a waiver for section 02 for all documentation requirements

Charo: If we waive requirements of informed consent and provenance of lines you are still going to need to provide the ESCROs with evidence of IACUC or IBS reviews. That is separate and will not be covered elsewhere.

Cibelli: That is routinely done for any project.

Charo: It is a check off sheet-the ESCRO is still going to be keeping track of the research at the institution-we don't want to have to recreate the dossier on where the donors came from.

Klein: Do they also need to document compliant with IACUC requirements?

Charo: I don't think you can waive the IACUC review because the source of the lines doesn't say anything about how they will be used.

Hall: Institutions will demand this.

Eggan: If an HFEA licensee is working with a SC lines, you actually have to have an HFEA license in the UK to work with hESC lines?

Charo: I believe so. Certainly to derive a new line.

Eggan: It could read that stem cells derived under HFEA licenses would all certainly be acceptable. That's desirable because if the enrollment tomorrow turns around and makes a SCNT cell line the that line would immediate be grandfathered in for use in CA. New lines produced in the UK would all then be acceptable. [If what is being said is true] anything that comes through the HFEA filter would be OK, including South Korean lines (if, e.g., Dr. Wilmut is successful in importing S. Korean lines that pass muster with the UK requirements]

Shestack: Would that be third party distribution?

Eggan: Yes. What we need to know is what type of stringency is being applied for the UK scientist to work with any cell line. It is well-established what is required in the UK to derive

new lines. Now the question is what is required of imported lines. Are these requirements the same?

Hall: Similar to what we would ask a local ESCRO to do—we will be asking the HFEA to do for us. We are accepting their standards for inclusion.

Charo: It looks as if the HFEA's role in regulating lines in the UK is comprehensive. [The HFEA Act of 1990 was aimed at creation, storage, and use of embryos in research, amended in 2001 to cover SCR]

Taylor: The IACUCs, IRB, and GCRCs all have ESC research review as part of their mandate. Waivers can avoid some of the up front hassle.

Hall: we might add "other mandated institutional review"—it's not our prerogative to waive other institutional requirements. Current wording does not exempt other institutional review. It's implied.

Kordower: Can be made more explicit?

Sheehy: According to state law all hESC research in CA requires IRB approval.

Charo: [Prop 71] exempts the CIRM from that law.

Sheehy: So there would be two difference enforcement tracks in an institution-one for CIRM-funded and another for non-CIRM funded research?

Lo: Need to distinguish between review and documentation. We are talking about two types of approval based on compliance with consent and compensation requirements-it is the documentation that is being waived. All other types of review that the institution or the rest of these guidelines may impose remain in place.

Eggan: After this discussion—the language should be "approved for use" rather than "derived."

Lo: To be clear we are not resolving the issue of who decides equivalency today. This issue and other difficult issues will be address [at a later date] and in the final guidelines.

This will be made clear as well in the public sessions.

Prieto: Request to change language from research "prohibited" to "not eligible for CIRM funding given that this is a funding agency not a research institution.

Hall: Need to make clear that documentation refers to documentation of informed consent and donor compensation.

[Public comment]

Peckman: The main issue is who has to maintain documentation or who is being waived from maintaining documentation. That is, the awardee institution. This has to state explicitly that you are waiving the requirement of the awardee institution from obtaining documentation.
"The awardee need not maintain or require the documentation."

[Consensus language inserted into CIRM Interim Regulations: NIH/HFEA/UK SC Bank cell lines " …do not require documentation by the ESCRO committee or equivalent body designated by the investigator's institution."]

Motion: To approve statement of equivalency- cell lines that are developed under standards equivalent to the UK Stem Cell Bank and other benchmark organizational standards if later approved by the SWG/ICOC as an equivalent, would qualify for the **waiver from documentation.**
Motion: Lansing/Klein
Second: Unclear
Motion approved unanimously

[Discussion of consensus language for "approved" research versus research "eligible for funding. Complete detail on eligibility will be provided in the CIRM Grants policy]

Consensus language:

Cibelli: How do you make sure that an investigator working with CIRM approved and non-CIRM approved lines does not use CIRM funds for work the non-approved lines?

Hall: If a problem is suspected, it will invite a CIRM audit.

Eggan [The NIH] has well proscribed accountability rules for the use of its funds and keeping one sponsored research project separate from another. A number of universities have collaborated to interpret the NIH rules to establish "stem cell facts and rules of the road" for doing eligible versus ineligible research. The CIRM could adopt similar rules.

Hall: Division of funds would be included in grants policy

Klein [to **Harrison**]: We can adopt rules for governing research (such as NIH's accountability rules) as contract provisions (rather than regulations?)

Harrison: Yes.

[Discussion of consensus language for "approved" research versus research "eligible for funding. Complete detail on eligibility will be provided in the CIRM Grants policy.]

Resulting Consensus language:

[Discussion on whether CIRM should required compliance to its guidelines for all embryonic stem cell research done at California institutions or just research using CIRM funds]
Option 1: Guidelines cover only CIRM-funded research: "if you want to spend [CIRM] dollars, CIRM can determine how you conduct yourself in the use of these dollars."

Option 2: Guidelines cover all hESC research-"if you want to spend [CIRM] dollars, CIRM can determine how you conduct yourself at all times."

Issues raised:

- Should the CIRM wallet be used to bootstrap non-CIRM funded projects into compliance with CIRM standards? (**Eggan**)
- If we are funding a project, we have the right to determine the guidelines under which that research is conducted, beyond that, [our reach is questionable] (**Hall**)
- Is the CIRM setting research standards for California? (**Sheehy**)
- If the NIH were to set up to require global compliance of its standards for NIH-funded and non-NIH funded research, the CIRM would not be able to fulfill its charge (**Hall**/**Klein**)
- How will compliance be enforced? (power of the purse)
    - NIH policy of ensuring compliance-through single project assurances-they ensure that NIH funds are not used for research on non NIH approved lines, directly or indirectly
- All the taxpayers expected us to do is set up guidelines for how their money was going to be spent (**Lansing**)
- The public has an understanding that SC research is happening in California because they voted for Prop 71. If we do research that the public isn't comfortable, we are inviting the legislature to come in an adopt a parallel set f guidelines, whether they apply to our funding or not. We risk having multiple layers of guidelines which is problematic in terms of establishing assurances of compliance(**Sheehy**)
- What is the relationship with the committee created by SB 322 which is currently inactive?

No consensus language on this issue arrived at at this meeting. Remains to be addressed fully by the SWG.

[see transcript pages 135-146]

[Clarification sought on why the ESCRO committee cannot be a subcommittee of the IRB]

The CA legislation made a mistake in placing hESC research within the purview of the IRB. The IRB has no expertise in the area of basic science that does not involve human subjects.

This issue has a political landmine hidden within it because of the long-running debate over whether or not an embryo should be defined as a human subject.
Up until now, they are not. This administration is looking carefully at this definition and taking a step toward classifying embryos and embryo byproducts as human subjects. This language in the NA Guidelines is there so that IRBs are not required to review subjects beyond their expertise.

Shestack: Why does [the relationship between the IRB and the ESCRO] need to be specified in the Guidelines given the California law that governs research at California institutions.

Eggan: Given that institutions outside of California will be adopting the NA Guidelines, CIRM will want to have an equivalent structure to the rest of the country. It is critical, as well, that embryos not be perceived as human subjects.

[Discussion regarding whether Guidelines language reference "a preexisting committee may serve the functions of the ESCRO committee provided that it has the recommended expertise and representation to meet the requirements of this section" should be stricken]

Kiessling: We do not want to provide unnecessary (duplicative) layers of oversight—a way to do this is to not be concerned with whether an ESCRO is part of an IRB. You can say, if there is no human subject involved, then the ESCRO can be served by members of the IACUC.

Hall: Strongly urges this section to follow the NA Guidelines. We want to be consistent with the national institutions. The NA Guidelines worked hard to build recommendation that would meet with consensus and be applicable across multiple institutions. We do not want to be premature in deviating from the model suggested by the Academies.'

[Discussion of the NA intent of the above language and why the composition of the ESCRO committee is described in the NA Guidelines.]

Charo: The intent of this language was to clarify the difference between human research and non human research because embryonic stem cell research involved both.

One way to comply with California law [requiring ESC research be reviewed by an IRB] is to call an ad hoc committee of experts that could advise the IRB (as is routinely done with IRBs) In this case they would just defer to the ESCRO and "rubber stamp" the finding of the ESCRO to be in compliance with CA law.
The ESCRO committee replicates some of the work of the IACUC and IBC. There is a debate about its usefulness.

Eggan: Harvard has decided that the IRB must review all SC research, but ONLY to say whether or not there is a human subject in that research to protect in that research. It makes a determination of whether the research is exempt from IRB review.

Klein: This language could be designed to protect the ESCRO from the political influence of the IRB.

Sheehy: How can the ESCRO fulfill its function fully if its relationship is severed from the IRB. Why set up a dual set of standards where all other stem cell research in CA is required to be reviewed by the IRB and CIRM funded research must be reviewed by an ESCRO committee that is separate from the IRB?

Charo: This would not be the case if it were an ad hoc committee, not a subcommittee of the IRB. It is not subject to the Common Rule regarding quorums, meetings, and documentation. As an ad hoc committee, you're delivering your advice to the IRB.

Motion: To remove the language in Section 06(b) "**a preexisting committee may serve the functions of the ESCRO committee provided that it has the recommended expertise and representation to meet the requirements of this section"**
Motion: **Klein**
Second: unclear

[Public comment]

Peckman: Given what it takes for an institution to set up this kind of ethical infrastructure (ESCRO) to be in compliance with guidelines, advises being very careful with what is established in the interim. Would strongly encourage deferring a decision until after [**Peckman**'s] presentation because it gives broader perspective on what has been discussed in terms of implementing guidelines that recognize the purview of IRBs, IACUCs, and ESCROs. Getting something solid that institutions can use ultimately over a long period of time is crucial.

Susan Fogel: Strong statement that decisions made by the SWG not undermine reproductive rights of women in CA. Anything hat recognizes an embryo as a human subject will go farther than the work funded by the CIRM. Appreciates the impetus to not create unnecessary layers of oversight administration, but be aware of Prop 73, which seeks to redefine when life begins which would impact the work of this committee. Creating too close a linkage between an IRB for human subjects and elevates the status of embryos would be disastrous.

Reed: Concern that what has been discussed suggests that the actions of the IRBs will not be influenced by the bureaucratic centralization trend at NIH and impact research at the CIRM negatively. It would be easier to tighten guidelines at a later date than loosen them.

Movement to hear Steve **Peckman**'s presentation and the institutional perspective on the role of IRBs, ESCROs, and implementing guidelines.

Lansing motion, given time constraints, to defer the question of the language in 06(b) and Steve **Peckman**'s presentation in order the ensure that salient issues of the interim

guidelines are raised to gain sufficient consensus to pass interim guidelines to be recommended to the ICOC.

Motion: To defer the question of changing the language in the proposed CIRM Interim Guidelines, section 06(b)
Motion: Prieto
Second: Klein
Approved Unanimously

Lo: Other issues that members/public feel must be addressed before adopting interim guidelines? As distinguished from critical issues that will be addressed at a later date, after issue identification and extensive consideration by the working group.

Hall: We are discussing issues here with double vision—one is to pass interim guidelines to cover the training grants, the other is a long-term deliberative process to arrive at final recommended guidelines.

Shestack: Request to address the meaning of the NA Guidelines recommendation that institution engaged in SC research s**Hall**, at minimum maintain a registry
Will this be done by the CIRM, local institutions?

Charo: It referred to only institutions keeping track of lines being used at that institution

Shestack: So it is not a registry but a list of cell lines they are working with and their derivations as opposed to someone else who might, as a service to the research community, has a registry of all available cell lines.

Charo: Yes.

Prieto: Do these guidelines address other types of research that Prop 71 commits funding to?

Hall: This is an important issue for both adult and fetal stem cell lines-these are not covered in these proposed interim guidelines. We propose to examine existing regulations [that cover adult and fetal SC research] and bring a policy to a future meeting. So this will be an interim policy with respect to those lines. We will need to outline this in the Grants policy and hope that this working group will address it in its discussions.

Willerson: Recommend that the SWG consider placenta and cord blood cell in this category [with adult and fetal cells]

Taylor: The issue of compensation is an important one that time may not permit discussion of today but is practically very important.

Klein: Compensation is not permitted to derive new lines [for CIRM-funded research] under Prop 71. CIRM researchers could use other lines derived from non-CIRM funded institutions

which were created using donated oocytes that were compensated for if they met certain ethical criteria.

Lansing: We could not do this if we were only funding research institutions that adhere to CIRM Guidelines. This is an argument for not altering the current guidelines.

Lo: If you wanted to change the policy on compensation, it will require going to the legislature (after 2 more years), and getting a 2/3 majority.

Klein: We pay for expense but not missed wages.

Shestack: There is no compensation, just direct expense reimbursement. Are CIRM funded scientists doing CIRM-funded molecular biology allowed to use otherwise derived cell lines for which people may have received compensation?

Klein: Yes. As long as you met internationally accepted ethical standards with the consent and other issues.

Kiessling: Question on section 9 subsection (b): Institutions engaged in hES research s**Hall** create mechanisms for establishing central repositories for hES lines. What is you are not deriving any cell lines?

Charo: This is exactly the problem that arises when this is written not specifically for a funding agency but for multiple audiences. This banking section reads better if you are directly regulating institutions in your state. Suggest that the banking and distribution section [Section 10] be stricken from the interim guidelines and be revisited as we move toward a final draft.

Hall: This is encouraging people of put lines in banks (e.g., Melton's lines in the UK SC Bank), But the language may be superfluous in the guidelines.

Kiessling: This is only with newly derived lines.

Prieto: If we just accept this as an amendment, add the wording "s**Hall** create or participate in mechanism for establishing central repositories"—we want to encourage institutions to participate not necessarily establish their own.

Shestack: We do want to facilitate a methodology for making banking easier/more efficient

Prieto: We do want to encourage banking/dissemination.

Klein: This is constructive conceptual guidance for future CIRM funding ventures (GMP facility)

Charo: We have no business telling institutions what they should be doing. Our only business is in telling investigators what to they can and cannot do with our money. These

issues in the NA guidelines regarding banking were intended for the ESCROs, not the funding institutions-else there would be multiple guidelines out there (e.g., JDRF, CIRM, Michael J. Fox foundation re: how to deal with this issue) We do not want to lead institutions into impossible conflict in our effort to set good ethical guidelines.

Prieto: We do have a right to tell them what will happen with the biologicals that they create or derive with CIRM money.

Motion: To change the language of section 09(b) to read "institutions engaged in human embryonic stem cell research s**Hall** create or participate in mechanisms for establishing central repositories.
Second: **Klein**

Kordower: If a researcher is just using but not deriving lines, do they need to create a bank for those lines?

Prieto. No. The principle that we are trying to honor is information-sharing. There are two separate issues-one is banking, the other registry.

[Further discussion on wordsmithing language for banking section and whether it should it remain in the interim regulations as opposed to being deleted entirely per Alta **Charo**'s recommendation
See transcript pages 184-]
Key issues:

- NAS guidelines were aimed at ESCROs, not funding institutions (**Charo**)
- Should omit sections that will substantially change, else institutions will spend unnecessary work setting up ethical infrastructure based on the interim guidelines that are deconstructed later. We need to be as careful with interim standards as with the final standards. (**Charo**)
    - Caveat: Cannot give [institutions] interim guidelines and say that they do not have to follow them because they are interim and will change. If we are going to make substantive changes in a section, we should omit that section in the interim guidelines (**Eggan**)
- CIRM aims to gather representatives from different universities to get their perspectives on the proposed guidelines and to help avoid any unnecessary work on the part of institutions. This will be an open process. We have met with the UC Vice Chancellors of Research in which we talked about ESCROs. There is really 2 months of uncertainty (**Hall**)
- The banking section is poorly drafted-needs to be revised to be effective (**Cibelli**)
- This is a section in which adopting it will cause more problems than it solves-it should be tabled in the interim as one of the items to be developed. As written-this would prevent any researcher from getting a cell line to begin research. To not have this in the guidelines at this time would not inhibit research nor will it allow for faulty research to move forward. A registry can be kept at the laboratory level. (**Kiessling**/**Eggan**)

- Indicate that a library record of cells must be maintained at each institution and that this section [banking] is under development. There will be guidelines at a later point in time. (**Willerson**)
    - Stated as a motion
    - Seconded by **Klein**
- Critical to have a banking/distribution statement from the a patient advocate perspective patient -concern that striking the language at this point may impact how it is treated in policy statements later (**Shestack**)
- Proposed language for section 09(b)"Institutions engaged in human embryonic stem cell research s**Hall** be encouraged at present and possibly mandated in the future"…will allow institutions to get started on research training grants and indicates the direction we are going (**Kordower**)

Motion proposed by **Lo** seconded by **Prieto** to table this question of:

a) Adopting the banking section as is
b) deleting pages 7,8 on banking
c) Revising the language as suggested by **Willerson**, **Kordower**

Until the committee has heard from Steve **Peckman** and the banking and oversight study groups regarding a) the structure and function of ESCROs vis-à-vis the IRBs and 2) registry/ banking section

[See Peckman PowerPoint outlining the role of IRB/ESCRO committees within the context of CA state law at www.cirm.ca.gov under the SWG August 30 meeting or contact Kate Shreve at kshreve@cirm.ca.gov]

Narrative of Peckman's presentation can be found on transcript pages 205-221

Response:

- One can avoid the conflict [introduced by **Peckman**] of a two-class system by accepting the NA Guidelines as reasonable and that every CA institution should have an ESCRO regardless of CA law. It is not a bad thing that every research protocol be reviewed by both an IRB and ESCRO. This would facilitate a national standard. (**Eggan**)
    - **Peckman**: Not arguing for not having an ESCRO but in favor of flexibility that would allow multiple frameworks to accomplish the same goal.
        - **Charo** How to get the flexibility is the source of this debate. An alternative is to add to the language of ESCRO membership that there may be overlap in membership including staff.
        - Correction of **Peckman** slide: Derivation review is deferred to the IRB. The ESCRO wants confirmation that the IRB has done this but does not undertake de novo review of documents.

- By incorporating an ESCRO into an IRB you make it subject to the federal regulations that apply to the IRB-this would take flexibility away from the ESCRO

Peckman: The Guidelines are unclear on the overlap between IRB/ESCRO. There are several things that IRBs are currently required to review that don't involve human subject research. E.g., FDA law covering certain devices already approved by the FDA

[Further discussion on the role of the ESCRO/IRB; requirements of CA law that mandates IRB review of SC research and the Prop 71 exemption that exempts CIRM-funded research
Transcript pages 223

Key points: IRB/ESCROS

- NAS aim for the ESCROs was three-fold
  1)This would be the body that the research is going to all of the committees that need to review it
  2) Adds a level of expertise that isn't currently available-IACUCs could grow in this area
  -provides scientific justification for the development of new lines
  -provides review of scientific merit of work (e.g., animals and chimeras) outside the expertise of the IRB
  3) Political-the public can have some assurance that there is a mechanism to prevent things from falling through the cracks.

Agenda Item #7: Study Group Progress Reports

Overview of Banking study group: Key points (Prieto)

- **Key question**
  - Should the CIRM maintain a registry of SC lines?
    - Banking study group determination: Yes, there should be a central repository
    - Should this be subsidized to facilitate the sharing of lines which has been a historic problem in SC and genetic research

- **Key question**
  - Banking

    - Banking study group determination:
      - Important for the purposes of sharing information and maximize the distribution of lines-to ensue results within a reasonable time frame

- CIRM does not need to be the physical banker, this could be contracted out through and RFA mechanism
  - The RFA could read like the language currently provided in the NA guidelines
    - Question of whether this could be offered to an out-of-state body e.g., ATCC
- There should be a required time frame within which to deposit newly derived cell lines

o Oversight : Should each institution create a separate committee for oversight?
- Banking study group determination:
  - This should be the role of the ESCRO-there need not be a separate banking committee at each site if there were a central structure

o Tracking of identifiable cell lines
- Banking study group determination:
  - Should be the responsibility of the individual institutions-the source of the derived lines would be responsible for maintain personally identifiable information in accordance with HIPAA and IRB standards.
    - The institution would presumably manage the database
  - Cell lines should be coded so that donors could be contacted, if necessary
    - This would be overseen by the ESCRO and maintained at the institution

Hall: It is key that the various banks being established around the world be as transparent and comparable as possible to facilitate use of cell lines.

Bottom line: There needs to be a strong statement to the public and to the ICOC that banking is an ethical issue.

- Sharing standardized reagents should be a requirement for funding

Consensus language:

Section 100009 Banking and Distribution of hES Cell Lines

(a) Institutions engaged in CIRM-Funded hES derivation or research s**Hall** be encouraged at present and possibly mandated in the future to create or participate in central repositories for hES cell lines, including through partnerships or augmentation of existing quality research cell lines repositories, and s**Hall** adhere to high ethical, legal, and scientific standards consistent with Section 100009(a) and Section 100007.

(b) Cell lines derived or modified in any way with CIRM-funds are required to be shared through a well recognized stem cell bank that will make the lines widely available to

investigators. Cell lines derived or modified in any way with CIRM-funds are required to be deposited in a bank in a timely manner.

(c) CIRM encourages but does not require the following:

**Section 9A moved to Section 06(C)(6)-Registry requirement move to ESCRO section

Motion to approve consensus language
Passed unanimously.

Return to question of IRB/ESCRO: Motion was to delete the last two sentences in section 06(b):

Recap of salient issues in Steve Peckman's presentation

- **What impact would striking or not striking this language have on institutions?**
  Peckman- Institutions have already begun to implement structure in compliance with the current law. If you are going to proposed new guidelines that are inconsistent with this, they will have to change these structures in order to proceed with research currently being reviewed.

Klein: Having a statement that the ESCRO will not be a subcommittee of the IRB is an important one politically.

Charo: Changing language to say "may constitute an ESCRO committee from among the members and staff of an existing IRB"-perhaps even "may delegate ESCRO functions that directly deal with human subjects to an IRB"

- Signals that ESCRO is not directly reporting to an IRB-avoids being formally under 45CFR46 requirements
- Allows institution to leverage their personnel and their resources to the max while keeping some legalistic distinction that preserves the independence of the ESCRO

Eggan: I would hope that institution would take this seriously enough to find new personnel to populate the ESCRO committee to keep the distinction—if not new staff, then individuals whose backgrounds equip them to be thoughtful on these issues, not individual selected on the basis of convenience.

Olden: This is one of the design of the NAS committee in recommending the ESCRO to invite serious dialogue on these issues. The IRBs do not have the strongest reputations.

Kiessling: It is critical that we create this distinction that embryos are not human subjects.

Olden: Providing more work for the IRBs also set them up for failure.

Eggan: This other level of oversight will prevent problems with public confidence which will serve to undermine us the most.

Taylor: The separation of church/state-IRB/ESCRO is critical. Concerned about **Peckman**'s definition of human subjects as "having identifying information of a living individual" and the implications this may have on ESC research.

Charo: Any time you work with material that could be linked with an identifiable person, the person is potentially a human subject. The regulations now allow you to work with the material with the information that identified those individuals in a coded fashion—so long as the individuals from whom the materials came are not "readily ascertainable". These materials could be worked with and not require human subjects review.

[Public comment]

Reed: Need to be sensitive to national and state efforts to redefine the beginning of life at conception and how this may impact the way that we approach regulatory requirement for review.

Peckman: Encourages the CIRM to work closely with DHS to harmonize regulations regarding ESC research to ensure that there are not two layers of discordant requirements.

Tabled motion withdrawn by Klein/Sheehy.
Motion: To accept the language in Section 6(b) on ESCRO membership
Consensus language:

> A pre-existing committee may serve the functions of the ESCRO committee provided that it has the recommended expertise and representation to meet the requirements of this section. An institution may constitute an ESCRO committee from among members or staff of an existing IRB. The ESCRO committee, however, s**Hall** not be a subcommittee of the IRB

Motion: **Charo**
Second: Klein
Unanimously approved

Omnibus motion to recommend as Interim Guidelines the above approved text
Motion: Prieto/Lansing
Second: Olden

[Discussion]

Kiessling: Section 10(a): there is ambiguity about transplantation, differentiated derivatives not requiring ESCRO review.

Charo: The NAS' goal was to point to the fact that the fact majority of purely lab studies that don't involve identifiable tissue, animals, recombinant DNA could be waived. The language is awkward.

[Discussion on framing the question of ESCRO review in section 10(F) see pages 272-280]

Motion: To delete section 10(F)-on the basis of confusing ambiguous language
Motion Kiessling
Second: Kordower

Unanimously approved

Return to Omnibus motion to recommend as Interim Guidelines the above approved text
Motion: Prieto/Lansing
Second: Olden
Unanimously approved

Agenda Item #7: Study Group Progress Reports Cont'd

Interstate and International Collaborations: Key identified issues (Charo)

Overarching questions: How to facilitate collaboration

- **What are restrictions on materials from outside CA/USA**
- **What are the minimum ethical standards we want to apply?**
    - Equivalence has two parts:
        - 1) substantive rules
            - I.e. informed consent—but from whom (what to do about anonymous donors?)
            - no compensation-including no lost opportunity cost reimbursements
        - 2) Procedural-who decides the criteria for equivalence?
            - What is the minimum standard?
            - Who measure other institutions or national laws to determine whether they meet those minimum standards?
- To what extent do these restrictions apply to the work of ancillary researchers such as biostatisticians? (Requirement that they work with data based on ethically derived materials)

Proposal:

- **We focus on the requirement that CIRM researchers work with materials that determine are "ethically derived"**
- **Anything that was derived in accordance with the extant laws and ethical norms of an area be presumed to be ethically derived unless the ESCRO suspected otherwise. (Benefit of the doubt given to lines derived in accordance with local law and regulation in other places.**

Preclinical Research Standards Study Group: Key issues(Kiessling)

- **[See preclinical research standards Study Group outline]**
- **Charge of the Study Group**
    - Consider sources of SC research and therapeutic potential
    - Tests of efficacy and safety in animal models

- **Considerations a given to possible sources of stem cell-bone marrow, skin, olfactory neurons, cadaverous tissue, fetal, cord blood, placental including relevant laws**
- **Controversial areas:**
  - **Eggs fertilized for SC derivation. This is not permitted in Canada-is thus far allowed for the CIRM. There may need to be some justification for creating embryos for research purposes.**
  - **SCNT**
  - **Introducing ESCs into embryos of other animals**
    - **4 states have adopted laws on this**
    - **Needs further review**

Action: Request that the committee (SWG) review the outline of this study group to consider these issues for further discussion

Donor Recruitment and Protection: Key Issues (Lo)

1) **Recruitment:**
   Consent for oocyte donation
   - Consideration of those undergoing oocyte retrieval for fertility treatment
     - Could the oocytes not being used for family building be donated to researchers?
     - How to ensure true informed consent and possible setbacks to reproductive goals

2) **Compensation for injuries that are the direct result of participating in oocyte retrieval for research purposes.**
   - Desire to separate short-term (OHSS) versus long-term adverse effects
   - Prop 71 states that compensation can only be for out-of-pocket expenses.
   - Federal guidelines usually provide no clause for compensation.

Issue: We are not compensating women who donate oocytes for research for anything but their out-of-pocket expenses, should they or their insurers bear he cost of treatment for compensation for research-related injuries. This is a potential inequity.

Broad SWG Issue: We need to work on diversity language regarding donors and access to treatment.

[**Lo** provides an overview of proposed timelines and work plan for the immediate future for the SWG toward the goal of finalizing the CIRM Guidelines for formal review by the OAL]

August-September:
Public session to receive public comment on the CIRM Interim Guidelines
September 9:
Review of CIRM Interim Guidelines by the ICOC *(This was deferred to November 2)*

October-November-December
2 additional meetings of the SWG
Submission of final guidelines to the CA Office of Administrative Law
Formal 45 day public comment period

- SWG can comment during this period-substantive changes will invite an additional 45-day comment period
  - Consistent with the 270 day period within which we are bound to adopt final regulations, substantive changes may present problems in meeting this goal
- The submission might be able to be submitted in a modular fashion-section by section-- which may allow for section to be worked on concurrent with the APA process –this will be confirmed with the OAL

Spring
Possible further review by the SWG following the APA process

Motion for Adjournment: Lo
Kordower: Second

[Meeting adjourned 17:46]