Meeting Minutes
Scientific and Medical Accountability Standards Working Group
October 24, 2005
Luxe Hotel
Los Angeles
10AM-6PM

Attendance:

Working Group Members

Jose **Cibelli**
Kevin **Eggan** (via teleconference)
Ann **Kiessling**
Robert **Klein**
Jeffrey **Kordower** (via teleconference)
Sherry **Lansing** (co-chair)
Bernard **Lo** (co-chair)
Ted **Peters**
Francisco **Prieto**
Janet **Rowley**
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
Jennifer Rosaia, CIRM staff

[Welcome, Sherry Lansing]

[Roll call]

Agenda Item #4: Approval of Minutes from August 30, 2005

No corrections or comments.

Motion: To approve minutes from August 30, 2005 meeting with corrections
Motion: Willerson
Second: Kiessling
Motion passes unanimously
(To view approved minutes, please go to www.cirm.ca.gov)

Agenda Item #5: CIRM Staff Report

Geoff Lomax provided a staff progress report outlining the following:

- Recommended new members
  - Patricia King, JD (ethicist)
  - John Wagner, MD (scientist-clinician)

  (see brief bios attached to the agenda for this meeting under "CIRM past meetings": http://www.cirm.ca.gov/meetings/2005/10/10-24-05.asp)

- Interim CIRM Regulations
    - Including recommended revisions to change the wording in section 100007(L)(2) to restore the original meaning intended by the NAS committee that was inadvertently changed in the process of converting the NAS Guidelines to regulatory language appropriate for CIRM use.

        - Original Language from NA Guidelines
          "In addition, donors could be offered the option of agreeing to some forms of hES cell research but not others…"

        - Section 100007(L)(2): Interim CIRM Regulations Language with deviation from NA Guidelines

          "Donors shall be offered the option of agreeing to some forms of hES cell research but not others…",

Since most universities do not currently impose this requirement as a rule, this language would introduce a requirement that present a substantive and unnecessary change to existing practice. Recommendation: To restore original language.

- Update on the public sessions held in Los Angeles (August 31); Sacramento (September 20), and San Francisco (September 27) (see summary of public comments attached to the agenda for this meeting under "CIRM past meetings": http://www.cirm.ca.gov/meetings/2005/10/10-24-05.asp)
- Timeline for drafting final CIRM Regulations on human embryonic stem cell research.

(see Geoff Lomax PowerPoint entitled "Staff Report for 10-24-05" under the minutes for this meeting at http://www.cirm.ca.gov/minutes/)

Agenda Item # 6: Discussion of Form and Framework of Draft Recommended Regulations

Bernie Lo framed the discussion of formulating ethical principles into regulatory framework.

- Key points
    - Regulations need to be flexible to accommodate the developing science and must not be overly prescriptive
    - Must also balance the need to be clear and functionally effective for research scientists and institutions to know what is required of them in order to be in compliance with the regulations
    - Importance of ensuring that regulations serve the ethical regulatory purpose without posing an undue burden
    - Regulations should be sparse—recognizing that we are limited by California law in terms of putting anything substantive or binding in a preface or supplemental guidance. This deviates from the federal model of writing regulations.

Overview by James Harrison on what the California Office of Administrative Law requires of regulations.

- The OAL reviewed the CIRM draft regulations and considered them to be a good foundation for effective regulations
- The California Administrative Procedure Act is more expansive than federal law
    - The CAPA prohibits state agencies from enforcing any guidelines or criterion, bulletin or manual that sets forth rules unless those rules have been adopted as regulations. If rules are imposed outside of the regulatory process, they are considered "underground regulations" and which are in violation of the CAPA.
        - Most of case law in CA in involving the APA involved attempts by agencies to use forms or manuals or bulletins to supplement or embellish the regulations.
        - E.g., quarterly progress report forms associated with the grants process may not include additional reporting requirements

Conclusion: The CIRM must think very carefully about the rules it wishes to set forth. All of these rules must be included in the regulations. We are not permitted to add to them subsequently except by amending the regulations [via the APA process]
There are ways to expedite the review and adoption of amendments to regulations—but they must go through the formal rulemaking process.

- APA requires a 45-day public comments period followed by 30 days of OAL review
- There are circumstances where the enactment of a regulation is necessary to preserve the health, safety , or general welfare of the public, and amendments to regulations can be adopted as emergency regulations. This involves a five-day public comments period and a ten day OAL review.

Shestack: Do all administrative requirements of grantees [i.e. acceptable overhead, regularity of mid-cycle reports] need to be codified?

Hall: This will come under grants administration policy (GAP) which is in development. It will not be [directly] addressed by the Standards Working Group given that they do not deal with ethical issues but administrative policy.

Shestack: Some items that are currently being considered under the GAP may be considered by members of the Standards Working Group. Currently the effort [of writing the GAP] is staff driven. [There is concern that the medical and ethical standards that are being addressed by the SWG is narrowly defined] For example:

- Having the requirement (in the GAP) of reporting negative results.
- Issues that deal with CIRM mission and strategic planning

Klein: Are you permitted in the grants policy to present a range of options for reporting that are dependent on the type of grant?

Harrison: If you are leaving the ultimate determination up to staff to exercise discretion without objective criteria provided, this would be open to being challenged regarding whether grantees know how to conduct themselves.

Klein: Since there will be individual grant contracts, there will hopefully be the opportunity to individualize a contract and not have the terms of the contract be a regulatory document.

Harrison: If you are talking about an agreement that applies to only one individual as opposed to a class of individuals, it does not have to be adopted as regulation. If they [are policies and procedures that] have uniform application, [then they would be considered regulation]

Hall: The question has arisen about how we will enforce [the CIRM grants policy]. The CIRM will require awarded institutions to read the CIRM GAP and sign a statement indicating that they agree to abide by its terms. If institutions are found to be in violation of the grants policy agreement, the GAP address penalty actions. There may be cases (particularly in the case of private industry, where CIRM will write private contracts. We would prefer not to write individual contracts for each grantee institution. If an institutions wishes to received CIRM money, they will be required to comply with CIRM policies. We do not want to hold different institutions to different conditional requirements.
Klein: The [Prop 71] initiative allows for "enhancement" of the law by a 70% vote in both houses. An issue that may pose .e.g., an [unacceptable] administrative burden may be subject for such a proposed amendment.

Harrison: Regulations must be set forth in clear and concise language that can be readily understood by those who are required to comply with them. Statements of intent and aspirational language do not constitute regulations because they do not have binding authority.
[Aspirational] language can go into the "Statement of reasons" which is part of the public record that accompanies the regulations. The statement of reasons is designed to set forth the purpose and intent of the regulations and the rationale for their adoption.
One way to maintain flexibility is to use "performance standards" as opposed to "prescriptive standards. A performance standard is a regulation that identifies a goal and the criteria for achieving the objective but leaves open "how" the regulated parties comply with it.
A prescriptive regulation is a regulation that sets forth the sole means of complying with the regulation. It is specifying the how institution are to obtain a goal rather than merely defining it.

Example: Performance standard for establishing informed consent. "Institutions shall obtain informed consent from donors for the use of their biological materials for research purposes."
Prescriptive standard: Describes explicitly the steps that an institution would need to follow to obtain an informed consent.
There are some cases where performance standards are called for and some where prescriptive standards are called for—the challenge is identifying the best approach [for each section of the regulations]

Lo: Existing California laws are very prescriptive [e.g., requiring specific disclosures during the informed consent process] It is not clear that the [current trend of having] longer and longer consent forms help the participant to comprehend the research protocol.

Hall: The challenge is to identify those areas that you want performance on—and allow people to carry out that standard as they wish—allowing for more prescriptive standards that at least meet the performance standard.

Harrison: correct. The twin challenge is to make a performance standards clear enough for those regulated by it to understand how to be in compliance with it. E.g., you may not simply use language such as "the ESCRO must evaluate whether the research is 'ethically appropriate'" because what is ethically appropriate does not give a clear enough definition of what measures of evaluation should be used to deem a practice or protocol "ethically appropriate'. We want to both set a performance standard that is somewhat flexible while at the same time being definitive enough to pass Office of Administrative Law Review.

Hall: While you cannot have a manual (as a guide to the regulations) that describes what is and is not acceptable, you may give example and counter examples [of best practice]?

Harrison: This is risky. 1) if a negative example is not clearly set forth in the regulation or not evident to those who are trying to comply with it, the OAL would say you have adopted an underground regulation 2) If the institutions believe that these examples are "exhaustive" and required, the OAL might also determine that you are using the manual and examples therein as a way of imposing new rules on the institutions.
This can be done but must be done very carefully. You should leave out examples of what is not acceptable lest it be considered by the institution(s) binding guidance. You must be clear that examples that you use in the guidance/manual do not represent exhaustive examples.

Lomax: There is an opportunity to cite existing law in the regulation. When you cite a federal regulation, you are citing the regulation in effect on the date of your citation—were that law to change it would not be a preemptive ruling.

Harrison: If we cite federal law in the regulations, we would want to specify that we are referring to the federal reg in effect as of the date that the regulation is adopted.

Agenda Item #7: Issues to be discussed at this meeting of the Standards Working Group include but are not limited to:

- **Consideration of ESCRO membership**

Lo: There are 3 different ways we can put information out to grantees and to the public
E.g.,:

1) In the Statement of reasons-gives rationale for the regulation we're writing
    a. Why do we have ESCROs (see NAS preamble)
    b. Why do we want flexibility in the regs—so that institutions can design what works best for them and even arrive at best practices.
2) In the regulations themselves.
    a. E.g., "The ESCRO shall assure appropriate oversight of CIRM-funded research including evaluation of scientific merit; evaluation of ethical appropriateness; and documentation of compliance with all CIRM-funded research at the institution.
        i. We might say recipients of funding must document that their institution has an ESCRO that can carry out the required oversight which has approved of their proposed protocol

b. "The ESCRO should have appropriate expertise to carry out its functions"
    i. Should include types of expertise?
    ii. Should include provision that a preexisting committee may serve the function of an ESCRO?
    iii. The ESCRO may contain IRB members but may not be a subcommittee of the IRB

3) In an accompanying guidance that gives examples that are non-exhaustive (understanding this is tricky)

Prieto: Does this mandate EVERY institution to have an ESCRO—should this be more general [to allow for joint ESCROs]

Lo: The language needs to allow for shared ESCROs.

Shestack: When may we discuss whether or not the CIRM should set up and encourage centralized regional ESCROs which would remove all of these questions

Hall: These would be allowed under the above schema but we do not prescribe whether or how institutions create such consortia.

Shestack: [In order to streamline the bureaucratic process] Why wouldn't the CIRM establish a centralized ESCRO to prevent smaller institutions from having the onerous requirements that might limit the participation of their talented investigators.

[Debate over the merits of a joint ESCROs as well as s who would run/manage a centralized ESCRO debated]

Klein: An option, given the limited staff of the CIRM, would be to fund a joint ESCRO.

Hall: The institutions will take their individual positions [on this issue] depending on their size and institutional needs—the reasonable approach would be to [write regulations that] enable institutions who have the resources to create their own ESCROs to do so while also making it possible for institutions to establish joint ESCROs.

Prieto: Proposed language: "An institution, group of institutions, or the CIRM itself may establish an ESCRO provided that…" this allows the regulations to allow for joint ESCRO relationship without being prescriptive as to whether it be the CIRM or individual institutions.

Cibelli: It is not clear who will supervise the ESCRO in the current regulations. That is a big hole.

Sheehy: At what point does ESCRO review take place? Before grants are submitted; before grants are funded?

Kiessling: We need to keep asking whether or not ESCROs are necessary-do we need to put another layer of review on each of these projects? Why did the National Academies recommend this layer of review?

1) IRBs do not necessary have the requisite expertise.
2) That oversight for human subjects research is kept distinct from hESCR.

If we create another committee on top of IRBs, which have enormous conflict of interest issues built into them—who is going to provide oversight for that committee (echoing Cibelli's argument). You would want this to be something that is done FOR and not BY and institution.

Rowley: [Clarifying the intent of the NA's Guidelines] The main concern of the NA committee was that 1) IRBs do not have the requisite expertise to review protocols for developing new cells lines as well as controversial experiments involving e.g., transplanting human cells into animal brains. The Academies did not deal with the issue of oversight of ESCRO committees.

Cibelli: If we are going to have ESCRO oversight—this working group should supervise the ESCROs.. If we have a centralized ESCR [as Kevin Eggan has brought up] the PI will be too far removed from the ESCRO committee and may run into difficulty getting protocols through the ESCRO

Hall: One significant issue is how close the ESCRO committee is to the investigator—if it is too close it could be argued that there is a conflict of interest. The most important feature in a regulatory process is to have effective communication between the investigator and the committee. Committees are most responsive when they are local.
In smaller institutions, the number of people with specialized SCR knowledge who could serve on an ESCRO equals the number of SC researchers—this is not the case at larger institutions. It is my belief that institutions should be responsible for research that is going on its grounds. In the event of legal challenge, an institution would, in this case, be in a position to defend its own decision. For a larger institution, a local ESCRO would be a better solution—for the smaller institutions, they could "band together." The problem with a centralized model is the question of who will run it.

Shestack: Review could be done post award.

Hall: IRBs do not want to review protocols that are not going to be funded-IH does not want to review grants that aren't going to pass IRB review.

[CIRM] is concerned whether the Grants Working Group will be able to handle the task of dealing with all of the grant applications that are submitted.

Shestack: Commercial IRBs?

Hall: These are, in general, not reliable. Their objective is money-making. It is not a solid foundation on which institutions should base their reputations.

Peters: If we are to keep ESCRO review at a local level, what about statewide oversight? Would it be worth considering having an "ESCRO of ESCROs" that would not keep track of every grant

but would be available if complaints were raised or if there were a problem of adjudication at a local institution, the statewide ESCRO would be the first court of appeals.

Rowley: From the NA perspective, there was consideration of a national ESCRO which would be more like a clearinghouse of people who have had problems which would be consolidated [and dealt with] at a national level. California would be well advised to have an ESCRO appeal mechanism in the event that an investigator feels he/she has been unfairly judged.

Sheehy: This conversation has seemed to be based on the assumption that large academic institutions will be the sole recipients of CIRM grants. There has been no recognition of smaller research institutions. The can end up setting up a barrier to participation. The liability issues raised [by Dr. Hall] are why consortia of smaller institutions are unlikely to be established because institutions are unlikely to assume liability. This scenario disincentivizes a company that wants to enter this field and compete for CIRM grants. It is not clear why CIRM would not put out an RFA to establish an ESCRO—if CIRM were to support the development of regional ESCROS, they would primarily draw from institutions in that region. There would not be the disconnect. E.g., northern CA and southern CA ESCRO. Communication would happen through informal networks that already exist.

Lansing: Can you mandate that this be one of the UC responsibilities.

Harrison: No.

Sheehy: CIRM could do this through an RFA mechanism. UC could apply for funding to establish these regional ESCROs. The CIRM will need to address the fact that SC research in CA is being funded by multiple sources. We know that there is a state law the requires all SC research to be reviewed by IRB, with the exception of CIRM-funded research. We need to have firm handle on the ethical soundness of what we are funding and could be the appellate body of last resort.

Kiessling: Institutions frequently have their own biases—if you are an institution in an institution that is opposed to SC research, you're not going to get your project approved [at that institution]. If you want to facilitate this work advancing in California, you will provide, not a regional committee, but a statewide committee which, in the electronic age, can give you a fast response. It would ensure uniformity in review and may give some investigators a "wedge" at their home institutions.

Willerson: Local institutions have the best ability to review SC grants-in the interest of simplicity, you could add members of [an existing IRB] to represent this ESCRO group . Rather than reproducing [the IRB model] There would be a small subset that comes to join and to consider stem cell research proposals from institutions. There will be complaints/disagreements which should be addressed by [either a statewide or regional ESCRO e.g.;] We do not want to set up more hurdles that result in producing disincentive.

Rowley: It is not clear hope many grants the CIRM will be getting—a single statewide committee may have to review 300 grants-it is unrealistic that a single committee would be able to do this in

a timely fashion Even if many of the grant applications will be less controversial requiring a lesser degree of review, but even if it is serving a bookkeeping function, it is a burdensome proposal. It is unlikely also to recruit capable investigators to serve on a central committee and spent several days reviewing grants for a central ESCRO./

Lansing: We would be condemned for not having ESCROs. We need to be mindful that we not limit who gets these grants and how do we help [facilitate research] at the smaller institutions? Could each institution be responsible for providing a reviewer(s) to central ESCRO responsible for reviewing protocols from smaller institutions [without their own ESCROs]?

Shestack: Who would review applications from industry?

Kiessling: 90-95% percent of are not going to require in-depth review. It would be easy to put a process in place for expedited review-particularly with electronic review. You would be well-advised to establish one statewide committee to get this process going and in 2-3 years break the process down into institutional committees.

Klein/Cibelli: The threshold issue is whether CIRM will require ESCRO review before it is decided whether there should be a central ESCRO and of whom it should be comprised.

Motion: To require some form of ESCRO for all CIRM-funded research
Motion: Cibelli
Second: Klein
Passes with a majority of votes.

Lo: What form then should the ESCRO review take: local versus regional/centralized model

The question is either to supplement or substitute for local review

Lansing: What does it take to set up an ESCRO

Hall: Expertise, money. It is not an ethical issue whether or not the ESCRO is local or statewide. It is administrative and scientific. The institutions themselves will want some input on this. The decision should be made at the institutional level. Almost all small institutions in the state have relationships with larger institutions. [These preexisting relationships] would make it easy for them to graft onto a larger institution's ESCRO-e.g., Buck/UCSF; Burnham/San Diego; City of Hope/USC. Institutions should be offered the choice—we should set the overall guidelines so that there is adequate ethical scientific review-that is out concern.

Prieto: Intrigued by Sherry's suggestion of requiring institutions to participate in a central ESCRO. We should put in general language that "an institution, group of institutions, or the CIRM may convene an ESCRO" to serve these functions and leave it at that.

Sheehy: I have a question of liability—some of the bigger institutions may not be willing to assume responsibility for another institution's research. It doesn't deal with commercial entities either.

Lansing: Could this committee serve as an ESCRO if there were no other option for an institution?

Peters: We want to accomplish to goals of an ESCRO with minimum obstruction. Could we say to an institution filing a grants application that here are the written guidelines of what is required of an ESCRO committee. It would be up to the institution as to how it would comply with this. (as an individual institution or consortium) CIRM would require that an institution check off all of the requirements. We would not have to monitor it unless a complaint was filed.

Kiessling: For the short term it is important to note that most of these applications are not going to involve human subjects—they will involve animal research. Each institution, if they are involved in any in vivo work will have an IACUC. Are you going to require that your institution have both supplements to its IRB and to its IACUC? IACUCs are composed of people who understand in many respects a lot more of the basic science behind stem cell work than human subjects review committees. So each institution has 3 bodies that are involved with every grant application:

1) IACUC
2) IRB
3) Research administration office

It isn't simply augmenting an IRB that would be involved in creating an ESCRO.

Peters: My point was to decentralize that schema [so CIRM wouldn't prescribe how an institution should be in compliance with the guidelines just demonstrate that they are.]

Cibelli: Supportive of an RFA mechanism for establishing a centralized ESCRO. The issue of liability can be simply addressed through a disclaimer. As soon as the institution is asking for money, they have to be responsible for how it is used.

Taylor: If there were an RFA that made it attractive [to the larger institutions] to oversee not only their own research but local industry and smaller institution-sponsored grants, you would have the best of all world. This should all be done on a more "just-in-time" as a condition of award.

Rowley: You do not want to underestimate the work of the ESCRO in the beginning. As an example, look at the discussion this committee has had—can you imagine this happening electronically? This will not work. The ESCRO will need to handle difficult issues which need to be done in person.

Klein: We [may want] to create mechanism that puts investigators whose institutions may object to their proposed research into a stronger position to negotiate with their institution. Second, you may want to require ESCRO approvals before accepting seed grant application.

Hall: This is not an ethical issue-it is an administrative one that we need to work out the pros and cons of—the requirements may be different for different types of grants. I don't see that the SWG needs to worry about [administrative issues] but should focus on the ethical issues before it.

Klein [in support of Prieto's proposal] creating these various options is a preferable approach to limiting ourselves to a statewide group or local institution because we want the broadest representation of research institutions all with distinguished faculties who may opt for different solutions to this process.

Dr. Hall recommended modifying Prieto statement to "an institution, group of institutions, or state agency, may convene an ESCRO" to correct for the fact that CIRM does not have the resources at present to support an ESCRO)

Prieto: Leaving the language open could include the possibility of putting out an RFA for creating an ESCRO.

Hall: This would need to be done very carefully—who would bid on the RFA, would private entities be permitted to bid. CIRM would then be liable should there be a problem with the ESCRO. This group is setting the standards and it should be up to the institutions to implement these standards. The role going forward is:

- To coordinate the ESCROS in the state
- Identify best practices.

If it is not working, we should have some mechanism for adjusting practice. If there is a national committee set up through the National Academies, we should be in close contact with them.

Motion: To include the language[under section 100003] "an institution, group of institutions, the CIRM or other state agency may convene and ESCRO
Motion; Prieto
Second: Klein/Willerson
Motion passes

Lo: Review of issues related to ESCRO policy discussed by the SWG

- The policy should be permissive (not prescriptive)-there should be broad option for ESCRO review-as determined by the institutions
- If there is just local review, should thee be an additional layer of oversight to determine if the ESCROs are working
- Should there be a mechanism for appeal if a institutional ESCRI denies a research protocol

Questions:

Hall: Do we require the institutions to have some arrangement for an ESCRO or an individual—an individual presumably cannot go outside of their institutional arrangement. Legally [CIRM policy regarding ESCROs] applies to the institution, not the investigator. So we should require any institutions that applied to the CIRM to have grants be approved by an ESCRO (either their own ESCRO, one that has been agreed to through their institution, or one that has been set up on a state level that they participate in.

Kiessling: The NIH position is that this is the job of the PI.

Hall: It is your institutions responsibility to have an IRB

Kiessling: I could go to a different institution-principle investigator driven research is very individual.

Hall The grant [in this case] is awarded to the institution, if you decide to move, the institution will let you move your grant, but the grant is to the institution.

Kiessling: If the institution accepts it. It is the PI responsibility to get the appropriate oversight.

Hall: The institution signs off on it. The NIH will not accept the grants unless the institution signs off on it. [per federal regulations]

Sheehy: Expressed strong conviction that the CIRM entertain 2 regional ESCROs-a northern and southern ESCRO. That would be funded by the CIRM through an RFA (so as to limit the use of CIRM staff resources. This committee should consider a centralized versus decentralized ESCRO rather than supporting a motion that is fundamentally decentralized without addressed the central issue.

Lo: This is then prescriptive.

Peters: [In the north/south ESCRO schema] would it be two ESCROs or a centralized ESCRO with two divisions?

Sheehy: If the RFA were written correctly, the committee would shrink and grow in accordance with the needs of the grants and the number of application in that field. Having a regional component (that would allow for face-to-face interaction) would be important.

Cibelli: It would be irresponsible for us to determine how many ESCROs are needed because we cannot anticipate the workload. This would not be conducive to getting quality reviewers.

[Public comment]

Don Reed: Opposes any further layers of bureaucracy. If an ESCRO is determined to be useful, however,- would recommend including language that the ESCRO cannot override the CIRM's decision and that the decision on ESCRO involvement be made on an individual basis—e.g., why take up additional time for non-controversial research.

Motion voted on and approved

Motion: Include that an RFA will be issued to create a statewide ESCRO that would serve for industry, for smaller institutions who cannot support their own ESCRO or may not wish to create one

Motion: Sheehy
Second: Peters

Discussion on the motion

Peters: Would those who would go to a statewide ESCRO do so on a voluntary or mandated basis.

Sheehy: This would be used in the absence of one set up by their own institution. To allow investigators to be funded who do not have an ESCRO at their home institution.

Cibelli: How would this be dealt with in the case of institutions/small companies without IRBs.

Hall: Companies should pay for setting up an ESCRO as part of their business expenses

Klein: You could have a charge-based system such that when you apply for a grants, the grants includes the money to process this through the state-based system.

Taylor: As in university IRBs

Shestack: We have not addressed larger issues of industry use, streamlining the process for investigators/stakeholders. We are doing things as they've been done before and not being innovative. You could put out an RFP but this wouldn't stop the SWG or the ICOC from recruiting people to serve on a statewide ESCRO from various institutions or the private sector who would contribute to the ESCRO review. You may wish to go further in terms of laying out the implementation of this idea.

Sheehy: This issues could be run through the governance subcommittee. My issue is that I think we have created a barrier to [receiving CIRM funds] for researchers who may not have access to an ESCRO.

Hall: In order to move on we should bring this to the ICOC which has representative from industry, institutions, patient advocates.

[Agreement that language should be added that addressed the aspiration that no investigator (nor institution) be denied an opportunity to apply for a CIRM grant. To be brought to the ICOC in the SWG Staff Report.]

Vote on the motion

Motion: CIRM will establish or generate an RFA will be issued to create a statewide ESCRO to provide review so that no California investigator be denied access to CIRM funding.
Motion: Sheehy
Second: Peters
No vote taken

Consideration of Banking requirements
Lo: **Goals**

1) **To make a statement about materials sharing**
2) **Propose ways to establish an effective CIRM Bank**

To make a statement about materials sharing

- a. Cells (and cell based materials) derived through CIRM-funded research shall be shared with other investigators.
    - i. CIRM should make banking mandatory (Peters)
        1. could begin as simply as a computer website
            - a. could begin to centralize some information at the CIRM. It's not clear that the bank ever needs to have only one location as long as cell line availability is assured. (Prieto)
        2. should uphold the goal of access-to research and therapies (Peters)
            - a. we should start with where we would like to end up and consider how we will get there.
                - i. Banking will be tied to IP-the SWG should connect with the IP policy makers
    - ii. Must be careful not to have language that gives leeway for institutions to opt out of sharing policy (Shestack)
        1. Since there is currently no CIRM-funded bank, we need to give institutions options to satisfy the requirement today. If we decide to make it mandatory to put lines into a CIRM Bank established in the future, we would need to amend this language. This language will need to ultimately be revised (Lo)
    - iii. Need to be careful in expressing the wish to have materials submitted "in a timely fashion" because this would not be specific enough fro the office of administrative law (Harrison/Lo)
        1. **Options for establishing a timelines for submission of materials to the SC Bank:**
            - a. At the time of publishing-advantageous because background information would be publicly available (Lo/Hall)
                - i. This is the norm in academia
                - ii. For industry you would be applying a totally different standards
            - b. At the time of public disclosure-in the form of presenting an abstract (Taylor)
            - c. At the time of publication in a peer-reviewed journal (to avoid receiving a lot of weaker data/materials) (Cibelli)
            - d. 18 months post funding (Shestack)
            - e. Within 12 months after filing a (full) patent application (Klein)
                - i. This would allow researchers time to protect their knowledge
                - ii. This would be a big departure from NIH policy (Cibelli)

iii. Implicitly this suggest that if a researcher is acting with CIRM money, he must agree to mandatory research licensing (Shestack)
iv. It should be “at the time of filing of a full patent” this would be more equivalent for individual researchers and companies
v. CIRM needs to make sure that researchers declare when they have filed a patent (Sheehy)
    - There is no precedent for this type of disclosure
    - This leads to tricky IP issues
    - It will be important to get cooperation from the private sector to get (confidential) information on provisional patent filings to inform the deadline on which investigators will be expected to bank. (Klein)
    - This will likely be incorporated into the grants administration policy (Hall)
    - The taxpayers in CA have been told that this will lead to biotech opportunities and cures –tech transfer offices at universities have less incentive to publish a paper that includes a cell line that could be eligible for patent and the seed for a start-up biotech company if they are concurrently required to bank the line (Cibelli)
    - The same standards need to be applied to industry as to academic researchers (Kiessling) The regulations need to allow for both scenarios
        a. We want to make it possible to patent while ensuring that lines are available to researchers as widely as possible
        b. Researchers and biotech companies have difference aims. The researchers wants the cell lines as quickly as possible, the company needs to put the cell lines before venture capital before they are distributed to everybody
        c. This would require that a private company would have 12 months from the provisional patent to file a full patent-24 months in total. We would get to publication 6 months earlier (Klein)
            i. You would also have a materials transfer agreement in place so the technology can claim royalties. (Cibelli)

Issues:

- How to enforce sharing? (Hall)
- Cost can be a barrier to accessing lines-either through actual costs or IP entanglements that may prevent access (Sheehy)
    a. Need to add language about cost because you can assign a prohibitive cost to making the cell lines available
        i. "CIRM shall l fund the reasonable costs of making these cells available" (Lo)
        ii. "At CIRM-accepted rate" (Lansing)
        iii. These costs should not be underestimated (Eggan)
- Can be onerous and time consuming to distribute lines (e.g., Melton lab experience (Hall))
- CIRM needs to be explicit about establishing a bank (or a sharing mechanism) so that there is no room for institutions to opt-out (Peters)

Ways to establish an effective CIRM Bank

- The CIRM will establish a bank eventually (perhaps 2 repositories to spread the risk) (Hall)
- All banked materials should be derived according to ethical standards and (Hall)
    - The responsibility for determining how cells should be characterized and what standards they should pass through before being shared in the field as reagents would fall to the SC bank. (Hall)
- All banked materials should be well-characterized (Hall)
- The bank should be a research institute of its own to independently confirm the validity of all of the lines it houses-ensuring that lines are intact, viable and reproducible.—this will require a lot of money (Taylor)
- All banked materials must be screened for safety
    - This may need to be more clearly define as per the OAL requirements (Harrison)
- The bank will be the source of information for investigators-it will decide what information is distributed
    - The bank would be information source first. Second, it would handle physical distribution (Peters)
        - This would be more like a registry. The regulations have proposed both a banking and registry requirement (Harrison)
- Need to build in the language to make very clear the consequences if CIRM-funded investigators do not share their materials (Cibelli)
- Future funding by CIRM should be dependent on following CIRM Guidelines including the principle of data/materials sharing
    - The practice of sharing data/materials is a cultural phenomenon and dependent on the given field of research—we have an opportunity to set the norm for stem cell research in California that sharing is expected (Hall)
        - This will not happen because researchers in CA will have unique cell lines they will not share. (Cibelli)
        - The stem cell field is more altruistic-one could argue that Wi-Cell patents have allowed them to be more open—but the distribution has been more generous than in other fields (Taylor)

- History of a lack of sharing among researchers in the autism community drives home the importance of aggressively establishing this criterion at the inception (Shestack)
- Sharing should be extended to researchers outside of CA and not just to CIRM-funded researchers
- Lines need to be shared along with "fully enabling" information to allow research lines to be duplicated (Klein) The investigator needs to get his cell line qualified through the bank (Hall)
    - If people are not able to reproduce their research, their grant will not be renewed—this issue will correct itself (Cibelli)

- Regardless of their patent status, we are requiring that banked materials be made available for research use

[Further discussion on the issue of sharing materials—broadly speaking, the discussion considers the conflict between an investigators desire to maintain an edge and advance himself in the field and his desire to advance the field through sharing]

The CIRM needs to put guidelines in place that allows research to go forward until a bank is established. We need to define a) what is meant by published data and b) how are we to consider a commercial model?(Sheehy)

[Public comment on Banking]

Reed: Related a conversation with a UK scientist who stated the importance of having a central repository for cell lines and that cells were banks as soon as they were derived

John Wong: The committee is omitting a consideration of specialty media required to grow up cell lines—the disclosure should be expanded to include inventions that involve novel biofactors etc., that establish the glow-in-the-dark cell lines (referenced by Cibelli). These will also need to be considered in discussion of IP.

Consensus language arrived at:

Cell lines derived through CIRM-funded research shall be made available to other investigators within 12 months of filing a full patent or upon the date of publication of an article regarding the research in a peer review journal, whichever is earlier. Cell lines shall be made available in a manner to enable ["functional replication" or/and "full enabling replication"] of such lines. A requirement of ESCRO review or notification, consistent with the requirements of Section 100006, may be required as a condition of release of cell lines to other investigators [counter signature]. Cell lines may be made available through:

(1) the institution or investigator responsible for the original derivation;
(2) an designated stem cell bank;
(3) a CIRM designated stem cell bank

[Agenda Item #7: Consideration of Diversity language]

- Agreement that, in principle, establishing a statement of diversity is desirable

- Because there is not a clearly defined action associated with this statement it must go in the statement of reasons [which will accompany the regulations]
- We have struggled with a way to frame this aspirational language in regulatory form that imposes a requirement on institutions which is required by the OAL
  - Options :
    - To direct institutions that are governed by the regulation in reviewing potential donors to consider ethnic diversity of such donors
    - To make a recommendation to the Grants Review Working Group in funding research to consider the ethnic diversity of the research pool as a criteria [for funding] [Harrison]

The [CIRM] will also need to address the issue of diversity in its decisions to fund different categories of disease-how do you allocate funds to cover research on diseases that will affect a large number of people or orphan diseases you want to address?

Issues:
Diversity among:

- Donors
- Recipients-diversity of patient population
  - SCNT is critical tool: creating representational cellular models of disease informs us on genetic susceptibility in certain populations in addition to understanding and achieving histocompatibility (Hall)
- Targeted Diseases

Willerson: Be careful not to reinvent the wheel and take the NIH guidelines on diversity into account (inclusion of women, children, and minorities)

[Resolution on Diversity: SWG will not arise at draft language at this meeting but will request staff to research NIH policy; collect issues to add to this discussion for future meetings]

[Public comment on Diversity]

Susan Fogel: This does not address diversity among researchers. Why isn't there a section on research criteria that addressed diversity and funding criteria? Intent language is nice but means nothing and is rarely enforceable. Encourages finding an innovative way to incorporate diversity statement into regulations.

Klein: The goal of achieving diversity of researchers [and funding criteria] was explicitly addressed through the RFA for Training grants.

[Agenda Item #7:Consideration of Scope of Regulations being limited to CIRM-funded research]

Language proposed is taken from the Common Rule and is typically found in all state regulations of this sort [Lomax/Harrison]

[See consensus language in CIRM Draft Regulations]

Agenda Item #8: Consideration of Future Work Plan and Progress Toward Final Regulations

Issues to be covered: [as framed by Bernie Lo]

- **Informed consent**
  - There is criticism in the field regarding the length and content of existing informed consent forms—unclear if it achieves the goals to assure that participants are giving voluntary and informed consent.
  - The regulations need to address the voluntary nature of consent
  - The guidelines need to address the issue of [donor] recontact

Klein: We should consider if the SB 18 [Ortiz bill] can be harmonized with CIRM language on informed consent from the National Academies. May obviate the need for future legislations and avoid two different standards. Do we need a different standards for confidentiality related to nuclear transfer [to enable the development of disease/patient- specific clinical therapies]? E.g., The double encryption system used by the S. Koreans.

Rowley [NA perspective on confidentiality]: The NA Committee was mindful of confidentiality. In the UK SC Bank, they insist that they know the donors' identity—which is kept separate from all other information but can be linked. The FDA also requires that you know the donors—if we are thinking that fat down the line-why not start with that information employing a mechanism that ensures confidentiality of the donors' information? In the UK and Europe, It is required that if an investigator find a genetic variant or abnormality in the cell in the course of research, that information is required to be sent to the patient's physician. It is then up to the physician to make a decision about disclosure to the patient. The patient has the option of refusing disclosure

Sheehy: We might want to bring someone in with expertise on this issue.

Kiessling: Need to consider how to treat unexpected findings in the course of research [see imaging study example reference by Kiessling ppg 194-195 of transcript] which may impact a study participant's insurance status

Lansing: California law does not allow this type of information to be disclosed-an insurance company cannot drop you. This issue seems to boil down to three areas:

1) Confidentiality
2) Addressing what constitutes informed consent
   a. Intelligibility (Lo)
3) Coercion-pressure on women to participate in trials

Shestack: Can staff produce a sample consent form at least [for the procurement or derivation of cells] based on a number of extant examples?

Cibelli: [in agreement with Shestack] We should be setting the standard. Could grandfather the Bedford Research Foundation Guidelines.

Lo: The consent form is only one part of an involved process for oocyte donors that includes counseling, assessment of comprehension, and other procedural details to limit the risk of undue influence—by adopting a model consent form, investigators funded by the CIRM may not attend to the other aspects of the informed consent protocol

Kiessling: Do we want that level of detail [required of a informed consent template] in the regulations?

Taylor: We should out forth regulatory requirements for informed consent rather than boilerplate consent language.

Will the CIRM require the use of a template informed consent form or will flexibility be given to the research institutions? [AS in NHLBI, NCI]

Is the research moving too fast to make this approach impractical?

Lomax: There is an experimental subjects Bill of Rights [existing law in CA] which would cover informed consent in the clinical trial phase. [This will be circulated to the group]

Hall: What are the general principles that should be involved in a consent form?

- Disclosure to donor of all possible foreseen uses of donated materials (this may be changing, should not be specified)
- Donors should be aware that their donated materials will be used for research purposes as distinguished from clinical use.
- Possible medial risks/benefits
- Comprehension-evidence of informed and voluntary consent.
- Participants may choose to opt-out of research protocol at any time
- Disclosure of compensation for any research related injuries [See Prop 71]
- Consent must be intelligible
- Emphasize that a patients care will not be affected whether or not they participate in research

Kiessling: This will need to be addressed topic by topic-consenting a 6 month SCNT donor is different than consenting an oocyte donor.

Taylor: Confidentiality will be a difficult topic to address-we need to establish mechanism for recontact and protecting individual who do not wish to be recontacted. It will be difficult to predict what should be in a template form.

Sheehy: Do we consider the venue in this? E.g., what is the relationship between fertility clinic and research donors? Should sites for donating for research be separate [from IVF clinics e.g.,]?

Rowley: The National Academies did advise

a) to have a separation between research and clinical care, where possible.
b) Even if a couple states that they are finished with "family-building", all of the donor must be reconsented at the time that it is clear that there are embryos available for research purposes.

Lo: Did the NAS panel address the issue of oocyte donation in IVF practices as opposed to embryo donation in IVF practices?

Rowley: The committee considered it to be improper to donate fresh oocytes at that time because you don't know which of these may be able to be fertilized and lead to a viable embryo. "Leftover" frozen materials are OK.
Scientifically, the Korean work has demonstrated that fresh oocytes are more efficient for SCNT purposes.

Peters: Why would donating fresh oocytes be improper [at the time of extraction for IVF]?

Taylor: The issues are: 1) each ovary puncture [during the extraction process] carries theoretical incremental risk 2) Because of out inability to freeze oocytes in an effective way, any oocyte that is collected needs to be developed into an embryo.-you can end up with a lot of banked and frozen embryos that may ultimately be useful to a couple but may be in excess of what that couple is interested in using clinically. It is less clear that the size of the follicle is predictive of a viable pregnancy.

Lo: This raises the issue of problems with these types of reproductive decisions regarding fresh oocytes. If fresh oocytes are taken from an IVF center and the donor subsequently changes her mind about wanted more children or wanted to donate her oocytes for reproductive rather than research purposes, this is a dilemma.

Kiessling: This is on of the arguments in favor of having separate sites for donating oocytes for research from IVF clinics. IVF clinics are, however, where the expertise in this area of handling hormones is concentrated. It is possible that fertility clinics should not be involved in research protocol recruitment. The AAAS recommended [in 2002?] that

1) Recruitment for oocyte donation for research not be done in fertility clinics
    i. This could be considered a "bait and switch"
    ii. This would alleviate fears about human cloning

Lansing: What about the use of "excess embryos" from IVF clinics?

Rowley: Sherman Elias at Northwestern is reported to have a fair number.

Klein: Isn't one of the issues the method of freezing the oocytes [in terms of their viability and use for SCNT purposes?
Kiessling: The key is not whether the eggs are fresh or frozen but what type of informed consent was used.

Sheehy: The questions of whether informed consent for research should be done in the context of the IVF clinic. This is an ethical minefield.

Lansing: This is one of our biggest challenges. But the mission of this group is to make sure that informed consent is given [in the context of establishing CIRM-funded new SC lines]
How is the informed consent requirements enforced?
I don't want to limit a woman's ability to choose how her oocytes are used as long as she is making an informed choice.

Sheehy: Compensation disrupts choice [this becomes a problem when IVF clinics also extract oocytes from women for research purposes as well as reproductive purposes for which women can be compensated]

Kiessling: The Bedford program offers a course for which women receive a certificate. Women donating eggs for research could be required to take a course and be tested for comprehension. This could be a mechanism to ensure that researchers gauge comprehension.

Harrison: We need to first answer the question of who we are regulating-the donors themselves or the institutions. We need to know who is going to be governed by these regulations.

Summary of options/needs for the Working Group to come to conclusion on the issue of informed consent:

- General principles that should be in an informed consent need to be articulated
- Consolidate/review existing statues, laws, regulations that deal with informed consent
- Information-gathering on oocyte donors?
- What is the overview between the HIPAA Guidelines and the IRB Guidelines.
    - Review of HIPAA Guidelines (in light of the University of Pittsburgh decision not to review the Korean donor recruitment protocol)
    - Rowley: For HIPAA purposes , oocytes and embryos are not human subjects

[Public comment]

Don Reed: Cited example of HFEA required course required of potential egg donors to ensure comprehension. Stated importance of separating fertility interests from research interests. Wished to have "medical care for women who may suffer side-effects from egg extraction" to the list of provisions. Compensation fro injury isn't sufficient. There should be rules that protect women who wish to harvest their own eggs for their own fertility later (e.g., women undergoing cancer treatments that may leave them infertile).

[Issues that remain to be addressed on December 1]

- ESCROS: details of review
- Review of banking language
- Need to clarify issues around informed consent

- Intellectual Property-Review of IP Task Force Recommendations
    - Klein-including compassionate care funds or alternate models that promote access for low and moderate income persons
- Interim Grants Administration Policy Report

[Meeting adjourned 17:28]