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M E M O R A N D U M

To: Members, Governing Board
California Institute for Regenerative Medicine

From: James C. Harrison, Board Counsel

Date: January 21, 2012

Re: Institute of Medicine Committee Report on CIRM (Our File No.: 2297-0)

INTRODUCTION

On December 6, 2012, the Institute of Medicine ("IOM") Committee on CIRM issued its report on CIRM. Members of the Board, CIRM staff, and members of the public will have an opportunity to discuss the report at the Board workshop on January 23, 2013. In addition, Chairman Thomas plans to share his proposal to address the IOM's recommendations. Below, we summarize the background of the report, the IOM Committee's findings, and its recommendations. We have also included additional background information to inform the Board's discussion.

BACKGROUND

In August of 2010, the Governing Board approved a proposal to commission a report on CIRM from the Institute of Medicine. Specifically, the Board asked the IOM to examine:

- CIRM's initial processes: What can be learned from the history and process of building consensus in the public and scientific communities to support the inception and work of CIRM?

- CIRM's programmatic and scientific scope: Does CIRM have the portfolio of projects and grant opportunities necessary to meet its scientific goals? How can CIRM improve upon its existing array of programs? What additional programs

and initiatives are recommended to meet its goals? What impacts have been seen from international agreements? Does CIRM's scientific strategic plan address the range of relevant issues in regenerative medicine within CIRM's mandated scope of work?

- CIRM's organizational and management systems: Are the internal organizational and management systems (in particular, the board and working group structure and operations, the peer review system, the conflict of interest guidelines, and the grants management system) effective in working toward the institute's scientific goals? Are the systems that are in place scientifically and ethically valid and rigorous? Do they achieve the level of transparency and the level of stakeholder and scientific community involvement needed to meet the institute's public responsibilities and scientific goals?

- CIRM's funding model: Has the funding model for CIRM had an impact on the work of the institute? What are advantages of CIRM's model for covering long-term costs of medical research? Could aspects of this funding model serve as a paradigm for other states or counties? What has been the economic impact of CIRM's research and facilities' awards and grants?

- CIRM's intellectual property policies: What are the strengths and weaknesses of CIRM's policy for sharing revenues generated by intellectual property? How does this model compare to the model governing federally-supported research?

The IOM Committee on CIRM, which included 13 members, began its work in September of 2011. Over the course of approximately 14 months, the Committee: requested data, reports, and information from CIRM; held three public hearings; conducted site visits to the stem cell research facilities at UC Davis, UCSF, and Stanford; solicited input from various stakeholders through questionnaires, including a questionnaire directed to members of the Governing Board; held public meetings with scientists in Boston and Toronto; and interviewed more than 20 individuals.

SUMMARY OF REPORT FINDINGS AND RECOMMENDATIONS

In its report, the IOM Committee found, among other things, that:

(1) Proposition 71 was a bold social innovation;

(2) CIRM is both a creative supplement to more traditional funding models and an innovative initiative designed to further strengthen California's biotechnology efforts;

(3) The overall stability of CIRM funding has facilitated a longer-term outlook and thus the prioritizing of crucial long-term investments in both specialized facilities and human capital, producing substantial benefits;

(4) CIRM has attracted substantial additional private and institutional resources to stem cell research in California;

(5) CIRM's collaborations with funders in the U.S. and around the world have enhanced California's position as one of the key international hubs of activity in regenerative medicine;

(6) CIRM has carried out its mission at an ambitious pace, successfully and thoughtfully approving more than $1.3 billion in awards to 59 institutions;

(7) CIRM has been highly effective in building an impressive research portfolio;

(8) CIRM has done a very good job of creating and updating its strategic plan;

(9) CIRM has initiated energetic efforts to translate the scientific results of its programs to the bedside;

(10) CIRM has created an exemplary training program and seeded a pipeline of intellectual property and translational projects that are primed for industry involvement, outside funding, and unique therapy delivery mechanisms.

The Committee also made a number of specific recommendations regarding CIRM's funding model, governance, scientific processes, and intellectual property regulations, including:

1. Address the inherent conflicts of interest posed by the inclusion of Board members who are appointed from institutions that receive CIRM funds;[1]

2. Modify the grant application review process;[2]

[1] A summary of the appointments mandated by Proposition 71 is attached to this memorandum as Exhibit A. Please note that, contrary to a statement in the IOM's report, there are five seats designated for executive officers from campuses of the University of California, not nine.

[2] A summary of the current application review process is attached to this memorandum as Exhibit B. At the Chair's request, Scott Tocher has prepared a separate memorandum addressing the Board's voting record on applications for funding. This memorandum will be provided to you separately.

3. Consider changes to CIRM's conflict of interest policies;[3]

4. Sponsor research and training on regulatory and ethical issues, including RFAs addressing the ethical aspects of the clinical applications of potential stem cell therapies;

5. Establish a single Scientific Advisory Board, with a majority of members from outside California, to report to the President and advise him regarding strategic priorities, including RFAs, industry engagement, and portfolio balance;[4]

6. Develop a sustainability platform; and

7. Consider conforming CIRM's intellectual property regulations more closely to Bayh-Dole and adopting regulations addressing which state agencies will have authority to enforce regulations if CIRM is no longer in existence.

We have scheduled a Board workshop for January 23, 2013 to address the IOM's report in greater detail. Although members of the Board, CIRM staff, and the public may comment on any aspects of the IOM's report, we have asked the co-Chairs of the Intellectual Property and Industry Subcommittee to convene a meeting of the Subcommittee to discuss the IOM Committee's recommendations on intellectual property and to report back to the Board. The Chairman has conveyed his view that CIRM should maintain its existing policies regarding revenue sharing, pricing, and access. In addition, Chairman Thomas is working on proposals to address the IOM Committee's recommendations regarding a sustainability platform, but it would be premature to discuss these proposals at this time. Therefore, we do not intend to devote significant time to either the intellectual property or sustainability platform recommendations. Instead, we hope to focus the discussion on governance issues and the application review process.

We look forward to discussing the IOM Committee's report at our upcoming Board meeting.

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[3] A summary of the Board's conflict of interest policies and processes is attached to this memorandum as Exhibit C.

[4] This recommendation is within the President's jurisdiction and the President and his staff plan to respond to this recommendation, along with other scientific recommendations, including funding research and training on ethical and regulatory issues, made by the IOM, and report to the Board in the future. Therefore, we do not intend to discuss these recommendations at the workshop.

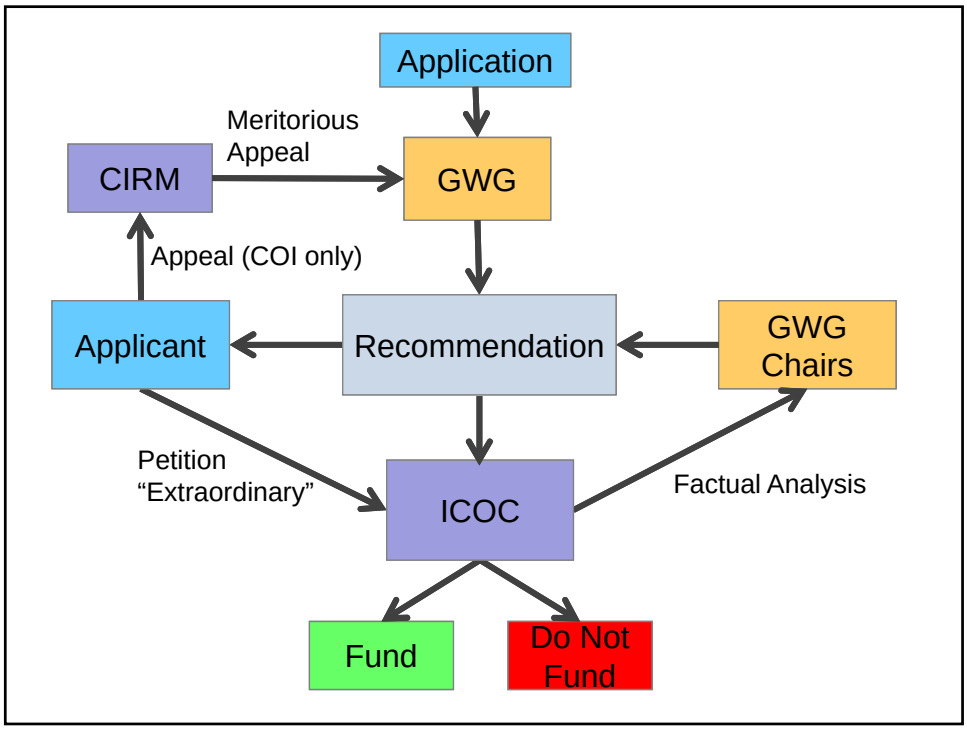
EXHIBIT A
Appointment, Nomination and Election of ICOC Members

Person Making Appointment	Appointee Criteria	Subtotal
Chancellor of the University of California at: San Francisco Davis San Diego Los Angeles Irvine	Appoints one executive officer from the respective campus.	5
Constitutional Officer Governor Lieutenant Governor Treasurer Controller	Each appoints one executive officer from each of the following categories: - A California university that is not one of five campuses of the University of California listed above - A California nonprofit academic and research institution that is not a part of the University of California - A California life science commercial entity	12
	Each appoints one representative from each of two California regional, state, or national disease advocacy groups.	8
	Each nominates one person for Chairperson and one person for Vice Chairman of the ICOC, each person meeting the criteria of the Act. (Health & Safety Code section 125290.20(a)(6)(A).).	
Speaker of the Assembly	Appoints one representative of a California regional, state, or national mental health disease advocacy group.	1
President Pro Tem	Appoints one representative of a California regional, state, or national HIV/AIDS disease advocacy group.	1
ICOC Members	Elect the Chairperson and Vice Chairperson of ICOC from the nominees made by the Constitutional Officers.	2
Total Members		**29**

EXHIBIT B

CIRM Review of Applications

Process Overview



Conflicts of Interest

- Conflicts of interest are considered for all reviewers, ICOC members, and CIRM staff
  - All personnel and institutions named in each application
  - Related business entities of for-profit institutions
- Reviewers disclose financial interests to CIRM for consideration of conflicts of interest
- CIRM staff and ICOC members file a California Form 700 of financial interests

Applicant Information is Confidential

- The identity of applicants and research proposals are treated as confidential material
  - Only the Project Title, Public Abstract, Statement of Benefit to California and Total Budget Requested are publically available
  - If approved for funding by the ICOC, then the name of the PI and institution are publically available
- Applications are not available to reviewers that have a conflict of interest with those applications
- All participants in a review sign a non-disclosure and confidentiality agreement

GWG Review Meeting

- GWG Members meet to score, evaluate and make recommendations to the ICOC.
- Meetings are held in closed session and limited to those necessary to conduct the review.
- Senior Review Officer presents the rules of confidentiality, non-disclosure, conflicts of interest and the process of review.
- Science Officer responsible for management of the RFA presents an overview of the RFA and review criteria.

GWG Review Meeting

- Scientific Review
  - Evaluate and score individual applications
  - Based on scientific merit
- Programmatic Review
  - Consider overall rankings
  - Consider programmatic objectives of RFA and mission of CIRM that would affect rankings and final recommendations

GWG Review Meeting

- During **scientific review**, the Chair of the GWG leads scientific members of the working group to evaluate and score individual applications for scientific merit.
  - Recruit 15 GWG reviewers w/ relevant expertise
  - Specialist reviewers participate via phone for ad hoc expertise needs
  - Each application is discussed (no triage)

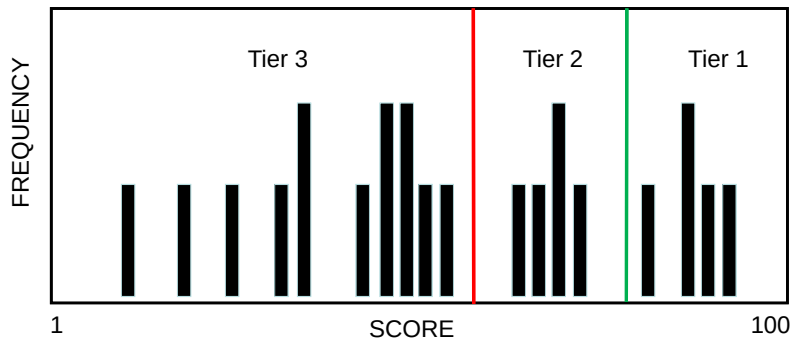
Scientific Scores

- 100 is highest and 1 is lowest score possible for overall merit
- All 15 scientific members of the GWG with no conflict provide a score – final score is average of individual members' scores
- Reviewers are asked to use the full scale in assessing merit
  - No specific weighting of criteria
  - Comments/critique should justify score.

GWG Review Meeting

- During **programmatic review**, the working group evaluates the entire group of applications taking into consideration the overall rankings by score, programmatic objectives of the RFA, and the perspective of patient advocates.
  - Vice-Chair (patient advocate) leads discussion
  - GWG sets initial funding tier thresholds
  - GWG may adjust rankings based on programmatic value
  - Make funding recommendations to ICOC

Distribution of Scores



GWG sets green line to mark initial threshold above which applications are scientifically meritorious (Tier 1). GWG sets red line to mark initial threshold below which applications are not scientifically meritorious (Tier 3).

Applications in Ranked Order – Initial Tiers to Begin Programmatic Discussion

	Rank	Score	App #	Title	Amount Requested
Initial TIER 1	1	90	0023	Project 1	$200,000
	2	89	1056	Project 2	$200,000
	3	85	0008	Project 3	$200,000
	4	80	1189	Project 4	$200,000
	5	76	0054	Project 5	$200,000
Initial TIER 2	6	70	1024	Project 6	$200,000
	7	68	0123	Project 7	$200,000
Initial TIER 3	8	60	1321	Project 8	$200,000
	9	55	1122	Project 9	$200,000

Green line

Red line

Applications in Ranked Order – Final Tiers After Programmatic Discussion

	Rank	Score	App #	Title	Amount Requested
Final TIER 1	1	90	0023	Project 1	$200,000
	2	89	1056	Project 2	$200,000
	3	85	0008	Project 3	$200,000
	4	80	1189	Project 4	$200,000
	5	76	0054	Project 5	$200,000
	6	70	1024	Project 6	$200,000
	7	68	0123	Project 7	$200,000
Final TIER 3	8	60	1321	Project 8	$200,000
	9	55	1122	Project 9	$200,000

Green line

Red line

Minority Reports

- If 35% of GWG members join in a minority position, a minority report may be submitted to the board with the final recommendations.
- The minority position must be stated, recorded, and agreed to by minority members during the meeting.

GWG Recommendations

- ***Tier 1: Recommended for Funding***
- ***Tier 2*: *Provisionally Recommended for Funding***
- ***Tier 3: Not Recommended for Funding***

Recommendation, score, and summary of review are provided to ICOC who make final decisions in public.

ICOC Meeting

- The ICOC meets in public session.
- The ICOC considers recommendations of the GWG and any information that is pertinent to making a funding decision.
- The final decision for funding or not funding is made by the ICOC.

What information is provided to ICOC and to the Public?

Prior to ICOC Meeting:

- Listing of applications in rank order by scientific score
  - the scientific score is the average of all individual scores given by the 15 scientific GWG members to that application
  - median, standard deviation, and range are also provided
- Copy of Review Report for each application (score, summary, recommendation)
  - Applicant names and institutions are not identified.
- Amount requested for each application and total requested for all recommended applications
- Any Extraordinary Petitions that were submitted by applicants

What information is provided to ICOC and the Public?

At the ICOC Meeting:

- Presentation of RFA concept, objectives, review criteria and approved budget.
- Display of applications in rank order by scientific score.
- Display of total budget requested and total approved for funding.

Consideration of GWG Recommendations

ICOC members identify specific applications for which discussion or information is desired.

- May request Science Officer to present brief summary of application and GWG evaluation
- May request Science Officer to address any questions or provide clarifications that do not involve proprietary/confidential information
- May request staff assessment or clarification of any Extraordinary Petition
- May discuss merits and programmatic value of application

Executive Session

ICOC may meet in executive (closed) session only to consider confidential or proprietary information related to applications.

- Members identify applications for which confidential information is needed to make an informed decision.
- Science Officer provides requested information referencing application data/figures as needed.
- Members do not discuss or evaluate merits of an application in executive session.
- Members return to open session after confidential information has been presented.

Consideration of GWG Recommendations

ICOC members may make a motion to move application to different funding Tier.

- Make motion to move specific application out of Tier 1 into Tier 3 (do not fund).
- Make motion to move specific application out of Tiers 2 or 3 into Tier 1 (approve funding).
- Members may discuss merits and programmatic value of specific applications.
- Members may consider public comments prior to voting on a motion.

Voting and Conflicts

- ICOC members do not participate in discussion or voting of applications for which they have a conflict.
- Members with a conflict are recused from executive session when ICOC considers confidential information related to an application.

EXHIBIT C
Summary of CIRM Conflict of Interest Policies and Processes

Conflict of Interest Overview

Like all state agencies, CIRM is governed by the Political Reform Act, Government Code section 1090, and other conflict of interest laws. Under the Political Reform Act, members of CIRM's Governing Board and staff are required to file annual Statements of Economic Interests (Form 700) and to recuse themselves from making, participating in making, or attempting to influence any governmental decision, including decisions regarding grants and loans, in which the Board member or staff member has a financial interest. In addition, Government Code section 1090 prohibits Board members and staff members from participating in any decision regarding a contract in which they have a financial interest.[1]

CIRM's three Working Groups – the Grants Working Group, which makes recommendations regarding research standards and awards, the Facilities Working Group, which makes recommendations regarding facilities standards and awards, and the Standards Working Group, which makes recommendations regarding scientific, medical, and ethical standards – are advisory only and therefore are not subject to state conflict of interest laws.[2] In order to ensure accountability and to prevent conflicts of interest, however, Proposition 71 mandated that CIRM's Governing Board adopt specialized conflict of interest rules for members of the Working Groups. These conflict of interest rules are modeled on, but exceed, the standards established by the National Institutes of Health and they arise out of recommendations made during a meeting convened by the National Academy of Sciences immediately after the

[1] Proposition 71 established an important exception to this rule to accommodate CIRM's specialized mission. Under Government Code section 1090, when one member of a Board has an interest in a contract, the entire Board is deemed to be interested in the contract and is barred from considering it. Proposition 71 was designed to draw upon the expertise of Californians with a history of: (1) managing large research grants and institutions and conducting major medical research; (2) understanding the critical path for the development and approval of successful experimental medical treatments and directing the development and approval process through the Food and Drug Administration and other regulatory bodies and ethical committees; and (3) advocating on behalf of Californians who suffer from a variety of chronic diseases and injuries. As a result, some of the members of CIRM's Governing Board are drawn from institutions that are eligible to apply for CIRM funds. In order to allow the Board to consider applications for funding under these circumstances, Proposition 71 includes an exception that permits the Board to vote on a grant award to an institution in which a member has an interest, provided that the member refrains from participating in, or attempting to influence the outcome of, the Board's decision regarding the grant or loan.

[2] Under the Political Reform Act, members of an advisory board are not considered "public officials" subject to the Political Reform Act unless the body to which the advisory board reports routinely adopts the advisory board's recommendations, over an extended period of time, without making substantive changes. (Cal. Code Regs., tit. 2, § 18701.) Proposition 71 avoided the uncertainty of this regulatory scheme by requiring CIRM's Governing Board to adopt conflict of interest rules modeled on rules promulgated by the National Institutes of Health for members of CIRM's Working Groups.

enactment of Proposition 71 to discuss best practices for CIRM. Members of CIRM's Working Groups are required to disclose relevant financial interests to CIRM and are precluded from participating in decisions in which they have conflicts of interest.

From its inception, CIRM has taken significant steps to ensure transparency and accountability. The Governing Board has adopted conflict of interest policies for Board members, CIRM staff, and members of CIRM's Working Groups that go beyond the requirements of state law. Under CIRM's conflict of interest policies, members of CIRM's staff are prohibited from holding an interest in a company that devotes more than five percent of its research budget to stem cell research and are barred from participating in a decision regarding a grant or loan to their former employer for a period of one year following the end of their employment. Similarly, based on a recommendation made by the General Counsel of the National Academy of Sciences, members of CIRM's Grants Working Group ("GWG") are drawn from outside of California to ensure they cannot personally benefit from CIRM funding, which is restricted to research conducted in the state, and they are prohibited from participating in the review of applications in which they have a professional or personal conflict of interest, in addition to a financial conflict of interest. The policies for the Board, CIRM staff, and the Working Groups are described below.

Summary of Conflict of Interest Policies

Like all state agencies, CIRM has adopted, subject to the review of the Fair Political Practices Commission, a conflict of interest code. CIRM's conflict of interest code requires Board members and staff to broadly disclose their financial interests in an annual financial disclosure form. These forms are made available to the public and the forms filed by members of the Board and CIRM's senior leadership are posted on the agency's website. CIRM has also adopted a Statement of Incompatible Activities which prohibits staff from engaging in activities that are inimical to, or in conflict with, their duties as CIRM employees.

CIRM has gone beyond the requirements of state law by adopting additional conflict of interest policies for Board members and staff. The Governing Board has adopted a conflict of interest policy that prohibits members of the Board from receiving any salary support through a CIRM grant or loan. In addition, CIRM has adopted conflict of interest rules for its staff, including the prohibition described above against holding investments in companies engaged in stem cell research and a requirement that staff members refrain from participating in the review of an application submitted by a former employer for a period of one year following termination of their employment. These rules are rigorously enforced and help to ensure the integrity of CIRM's review process.

CIRM's conflict of interest policies for members of its Working Groups are tailored to the functions of the particular Working Group. Members of the Grants Working Group, for example, are required to recuse themselves from participating in the review of an application submitted by a collaborator, someone with whom the member has authored a paper in the last year, and someone with whom the member is known to have a difference of opinion regarding a scientific matter, in addition to individuals and institutions with which the member has financial ties. Similarly, members of the Facilities Working Group are prohibited from

providing real estate facilities brokerage services for any applicant for a facilities grant, or for any entity that receives funding from the Facilities Working Group, and they are barred from receiving compensation from any recipient of CIRM funding grants. They are also prohibited from participating in the review of an application in which they have a financial interest, as well as an application that includes a project director or manager who is a collaborator of the member. All members of the Working Groups are required to submit financial disclosures to CIRM.

CIRM makes the records of its compliance with the conflict of interest rules available for audit. In 2008, the Controller conducted a review of CIRM's compliance with its conflict of interest policies and found that CIRM was in compliance.[3] The Controller also found that CIRM has "extensive conflict of interest policies that are modeled after and, in some cases, go beyond the National Institute[s] of Health requirements."

Conflict of Interest Procedures for the Review of Applications for Grants and Loans

CIRM has implemented rigorous conflict of interest procedures in order to ensure that all decisions are made on their merits and not due to any improper influence. The process begins with CIRM staff members and members of the Grants Working Group, who are screened for conflicts when applications for grants and loans are submitted to the agency. CIRM staff involved in the review process, GWG scientific reviewers, and GWG patient advocates are provided with a personal login and password to the CIRM Grants Management Portal website to complete their conflict of interest review. The names of institutional applicants, key personnel, and consultants associated with an application are provided to GWG participants, who review the comprehensive list and declare their conflicts before participating in a review. GWG scientific reviewers must also complete and submit a financial disclosure form that is examined for any possible conflicts of interest. Staff members and Board members who participate in the Grants Working Group disclose their financial interests on Form 700.

GWG scientific reviewers and GWG patient advocates who are in conflict with an application cannot view the application or be assigned as a reviewer of the application, and they are recused from discussing, scoring, and voting on the application. In addition, they are required to leave the room when an application in which they have a conflict of interest is discussed. CIRM staff in conflict with an application are recused from pre-award activities in connection with that application, and along with members who have a conflict of interest, they must leave the room during GWG discussion of the application.

At the end of each meeting, members of the GWG must certify, under penalty of perjury, that the member has not participated in the review of an application in which the member has a financial, professional, or personal conflict of interest.

[3] The Controller recommended that CIRM require the external scientific specialists with whom CIRM consults regarding applications to file post-review certifications attesting to their lack of conflicts, a practice that CIRM has implemented.

The Board has also established an extensive process to avoid conflicts. In advance of each meeting at which the Board will be considering applications for funding, CIRM staff provides each Board member with a list of all applicant institutions, principal investigators, and collaborating organizations and investigators (all without reference to application numbers) that would receive funding pursuant to the application. Along with this list, counsel provides a memorandum to the members describing the Board's conflict of interest rules and state conflict of interest laws and asking members to identify those institutions and investigators in which the member has a financial interest. Board members then submit a certified list identifying their conflicts to CIRM staff prior to the scheduled meeting. CIRM staff members also review each Board member's Statement of Economic Interests (Form 700) to screen for additional conflicts that a member may have overlooked. With this information in hand, staff compiles: (1) a master list identifying by application those members who have a financial interest in the application, and (2) a list for each member identifying the member's conflicts by application number. Each member receives a copy of his/her conflict list prior to the meeting.

At the Board meeting, the Board considers the rankings and recommendations of the Grants Working Group. Applications are presented by application number, without reference to the name of the applicant institution or the principal investigator. Thus, Board members do not know the source of the application when they vote unless the applicant self-identifies by filing an extraordinary petition or by offering public comments regarding the application.

Generally, the Board first considers motions to move individual applications from one tier to another (*e.g.*, from Tier 3 to Tier 1). Before a particular application is discussed, the Chair of the Board asks counsel to screen for members who are ineligible to participate in the discussion. Counsel reminds members to consult their conflict list before participating in the Board's discussion of a particular application. Staff members then monitor the discussion and the vote to ensure that disqualified Board members abstain, and when a roll call vote is taken on a specific application, conflicted Board members are not called.

The number of potential conflicts for each Request for Applications is often very large. In recent grant cycles, Board members, staff, and scientific reviewers have each had to evaluate over 200 potential conflicts. Such conflicts can exist at the institutional level (for example, the home university of an award applicant) and the individual level (for example, the Principal Investigator on an application). Generation of this list of potential conflicts has been a major focus of the IT spending for our grants management system. Today, the list of these potential conflicts is automatically generated, although each Board member, staff member, and scientific reviewer must review the entire list.

CIRM applies the same rigorous conflict of interest standards to the individuals whom CIRM asks to assist the agency in evaluating the scientific progress of its grantees and loan recipients. Thus, individuals who participate on CIRM's clinical and development advisory panel are subject to the same disqualification requirements as members of the GWG. To the extent that CIRM relies on other experts to provide guidance regarding its grants and loans, it will apply the same standards to ensure the integrity of its decisions.