TO: **Members, Science Subcommittee, Governing Board, CIRM**

FROM: **James Harrison, General Counsel**

DATE: **January 13, 2017**

RE: **Proposed Amendments to CLIN, TRAN, and DISC Concept Plans**

Background

The Board approved a concept plan for CIRM's Clinical ("CLIN") program on December 8, 2014, and additional amendments on July 23 and December 17, 2015. The Board approved concept plans for CIRM's Discovery ("DISC") and Translation ("TRAN") programs on July 23, 2015, and additional amendments on September 24, 2015, and December 13, 2016. The CIRM team has reconsidered these concept plans based on our experience implementing these programs and in light of CIRM's goals. Based on this review, the CIRM team proposes several amendments to the concept plans to further CIRM's goal of accelerating stem cell treatments to patients with unmet medical needs. The proposed substantive amendments are described below.

Proposed Amendments to CLIN, TRAN, and DISC Concept Plans

1. Good Standing Eligibility Requirement (CLIN, TRAN, and DISC)

CIRM has long requested that for-profit applicants submit information regarding their financial systems and, since 2014, CIRM has required the officers of for-profits to submit to background checks to determine whether an officer of the organization has been subject to criminal penalties for fraud or misappropriation of funds. Although CIRM, to date, has never had a need to disqualify an applicant based on this information, the eligibility requirements for CIRM's research programs do not currently empower CIRM to disqualify an applicant if CIRM determines that the applicant does not have adequate financial safeguards or if a background check reveals that an officer of the applicant organization has a criminal record involving fraud or misappropriation of funds. Similarly, CIRM has no mechanism to disqualify a proposed principal investigator who is currently under investigation for research misconduct or who has been debarred from receiving federal research funds. The proposed amendments to

the concept plans would add a "good standing" eligibility requirement. This would enable CIRM to disqualify an applicant if CIRM determined that: (1) for for-profits, and non-profits in existence for less than five years, the applicant did not have adequate financial systems in place to track CIRM funds, or the applicant's chief executive officer, chief financial officer, or principal investigator had been convicted of, or was currently under investigation for, crimes involving fraud or misappropriation of funds; and (2) for all applicants, the principal investigator was currently under investigation for research misconduct or was barred from receiving research funds by the Health and Human Services Office of Research Integrity. These changes would allow CIRM to avoid the costs associated with processing an application submitted by an applicant that is not in good standing.

2. **Eligibility for Small Molecule or Biologic where Stem Cell is Necessary to Manufacture the Therapy (CLIN 1 and TRAN 1)**

Under the current CLIN and TRAN concept plans, CIRM supports preclinical and clinical studies involving small molecules or biologics that act on or are dependent on endogenous stem cells for their therapeutic effect or that are dependent on targeting cancer stem cells for their therapeutic effect and that are being developed for a rare or unmet need unlikely to receive funding from other sources. CIRM proposes to clarify that research involving small molecules or biologics for which a stem cell is necessary to manufacture the therapy is also eligible for funding under CIRM's CLIN 1 and TRAN 1 programs.

3. **Program Manager Eligibility Requirement (CLIN and TRAN 1-3) and Principal Investigator Percent Effort (CLIN)**

Under the CLIN concept plan and the concept plan for TRAN 1 and 2, applicants are required to include a project manager on the applicant team to help ensure that the project stays on track and meets its milestones. With the Board's approval of the Translating and Accelerating Center awards, CIRM now has a Stem Cell Center that provides translational and clinical research services to CIRM awardees, including project management services. Rather than requiring applicants to designate an employee or hire an independent contractor, CIRM proposes to allow applicants to satisfy this requirement by entering into a contract with CIRM's Stem Cell Center where project management is a provided service.

The CLIN concept plan currently requires principal investigators to commit to a minimum effort of 30%. In some cases, however, for example the conduct of a clinical trial, the percent effort required by the principal investigator may be less. Rather than being prescriptive, CIRM proposes to modify the concept plan to require the principal effort to propose and justify a percent effort consistent with achieving the project's aims.

4. Readiness Eligibility Requirement (CLIN 1)

Currently, the concept plan for CLIN 1 requires that applicants be prepared to file an IND within 24 months of commencing work on the project. CIRM's goal, however, is to accelerate the time it takes a stem cell treatment to move from discovery into a clinical trial by 50%. In order to accomplish this goal, we must ensure that CLIN 1 awardees are prepared to file an IND/IDE with the Food and Drug Administration within 18 months of starting work on the project. CIRM therefore proposes to reduce the readiness eligibility requirement for CLIN 1 applicants from 24 months to 18 months.

5. Clinical Trial Eligibility (CLIN 2)

Under the current CLIN concept plan, small molecules and biologics that act or are dependent on endogenous stem cells or that target cancer stem cells are eligible for funding for all phases of a clinical trial. Because there is a well-known regulatory pathway for the approval of small molecules and biologics, a small molecule or biologic that has promising data after completing a phase 1 trial should be able to obtain funding from other sources to pursue further development. Cellular therapies, by contrast, face a far more challenging regulatory environment and may not be able to obtain sufficient funding for additional development even after obtaining positive data from a phase 1 trial. CIRM therefore proposes to restrict eligibility for phase 2 trials to cellular therapies where stem or progenitor cells either comprise the therapy or are used to manufacture the cell therapy. In addition, because a cellular therapy that has obtained positive data in a phase 2 trial should, in most cases, be able to attract additional funding, CIRM proposes to restrict eligibility for a phase 3 trial to cellular therapies where stem or progenitor cells either comprise the therapy or are used to manufacture the cell therapy and where the therapy is for rare indications (e.g., FDA orphan drug designation or Pediatric Investigation Plan). For phase 1 trials, CLIN 2 would continue to be open to a small molecule or biologic (**i**) that acts on or is dependent on endogenous stem cells for its therapeutic effect or that is dependent on targeting cancer stem cells for its therapeutic effect. CIRM proposes to clarify that a phase 1 clinical trial involving small molecules or biologics for which a stem cell is necessary to manufacture the therapy is also eligible for funding.

6. Award Caps (CLIN)

Under the current CLIN concept plan, awardees may not request more than $20 million for a CLIN 2 (clinical trial) award. To ensure that CIRM funds are spent wisely, CIRM carefully reviews the budget for each CLIN application and rejects budgets that are excessive. Based on CIRM's experience with the CLIN program and the need to ensure that CIRM has sufficient funds available to meet its goals, CIRM proposes to impose caps on all CLIN awards as follows:

CLIN 1 (Late-stage Preclinical):	$6 million (non-profits) $4 million (for-profits)
CLIN 2 (Clinical):	(1) Phase 1 trial: $5 million (for profits) and $9 million (non-profits)
	(2) Phase 2 trial: $12 million
	(3) Phase 3 trial: $15 million
CLIN 3 (Accelerating):	$15 million

7. Eligibility for CLIN 3

Under the current CLIN concept plan, CLIN 3 awards are available to existing clinical awardees who propose to undertake additional activities to accelerate the progress of their clinical project, such as manufacturing improvements and optimization. To date, CIRM has received three CLIN 3 applications but has not yet funded one. Based on the applications submitted to date, CIRM has concluded that this program is not well-designed to achieve CIRM's aims. CIRM therefore proposes to modify the CLIN 3 concept plan to offer an incentive to existing awardees that are able to convert an existing trial to a registration trial. This will serve the goal of accelerating stem cell treatments to patients with unmet medical needs.

8. Fundable Activities (CLIN 1 and 2)

Under the current CLIN concept plan, an applicant is barred from engaging in manufacturing activities beyond the manufacture of the candidate therapeutic sufficient to fund a phase 1 trial in the case of CLIN 1, or the proposed trial in the case of CLIN 2. There may be circumstances, however, in which it would be advantageous to manufacture more of the product than is necessary for the immediate trial. Rather than imposing an absolute bar on such manufacturing, CIRM proposes to permit an applicant to propose manufacturing activities for a follow-on clinical trial.

For CLIN 2, CIRM proposes to expand fundable activities to include comparability studies and commercial development activities. Currently, comparability studies are not authorized, but on occasion, the Food and Drug Administration will require comparability studies as part of the regulatory approval process. Similarly, in the case of a registration trial, for example, the Food and Drug Administration requires final formulation packaging and other development activities. Because CIRM's goal is to accelerate stem cell treatments to patients with unmet medical needs, it makes sense to permit applicants to propose such activities in their applications.

Of course, the proposed activities, including the budget for manufacturing, would be subject to CIRM review and consideration by the Grants Working Group and the Application Review Subcommittee.

9. **Eligibility for Devices (TRAN 3 and CLIN 2)**

Under the current TRAN3 concept plan, CIRM supports studies on a candidate device intended for use in the cure, mitigation, treatment or prevention of disease: (1) where the device is being developed for an intended use with human stem, progenitor or directly reprogrammed cells; (2) where the device is being developed for an intended use that addresses a critical bottleneck to translation, clinical development or use of human stem cell therapies; and (3) where testing with human stem, progenitor or directly reprogrammed cells confirms the utility of the device for stem cell based therapy development. In order to align the TRAN3 program with the CLIN program, CIRM proposes to expand the eligibility requirement for TRAN 3 to include studies on a device where the therapeutic mechanism of action requires the recruitment or incorporation of an endogenous human stem or progenitor cell.

In addition, the current CLIN concept plan imposes no limits on CIRM's funding of device trials. In light of CIRM's limited funding and the well-defined regulatory pathway for devices, CIRM proposes to limit device trials to feasibility. Therefore, CIRM funds would not be available for a pivotal trial for a device.

Requested Action: CIRM requests the Board approve the proposed amendments to the CLIN, TRAN, and DISC concept plans.

Attachments