CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

INITIAL STATEMENT OF REASONS FOR THE PROPOSED AMENDMENTS OF THE CIRM GRANTS ADMINISTRATION POLICY FOR CLINICAL STAGE PROJECTS

HEARING DATE: None scheduled.

CLOSE OF PUBLIC COMMENT: October 15, 2018

SUBJECT MATTER OF PROPOSED REGULATIONS: Amendments to Grants Administration Policy for Clinical Stage Projects

SECTIONS AFFECTED: The proposed action amends section 100503 to Chapter 5 of Title 17 of the California Code of Regulations, and the document incorporated by reference, the Grants Administration Policy for Clinical Stage Projects.

SPECIFIC PURPOSE AND FACTUAL BASIS FOR EACH AMENDMENT:

SECTION 100503 – GRANTS ADMINISTRATION POLICY for CLINICAL STAGE PROJECTS:

Purpose:

The purpose of Section 100503 is to describe the terms and conditions by which institutions who are California Institute for Regenerative Medicine ("CIRM") award recipients must abide during the term of the award.

Subdivision (a): This subdivision describes the scope of the regulation, indicating the regulation reaches all recipients of a grant, loan or guarantee from the California Institute for Regenerative Medicine ("CIRM") for late stage preclinical projects, clinical trial stage projects, and registration trial projects, agree to be bound by the terms and conditions of the CIRM Grants Administration Policy for Clinical Stage Projects incorporated herein by reference as identified below.

Subdivision (b): This subdivision identifies which provisions of the policy are being incorporated by reference. The CIRM Grants Administration Policy for Clinical Stage Projects is incorporated by reference herein in its entirety as to Sections "II" through and including "VI". As to Section "I," only parts "I.B.," ("Abbreviations"), "I.C.," ("Defined Terms"), "I.D" ("Types of Support") and "I.E." ("Roles and Responsibilities") are incorporated by reference.

Rationale:

Subdivision (a) is necessary to provide clarity in the scope of the policy – recipients of awards for Clinical Stage projects. Pursuant to the definition already provided in Proposition 71, the

regulation reaches all grants, loans or guarantees from the CIRM. The subdivision establishes the rule that all covered recipients are bound by the terms and conditions of the policy.

Title 1 of the California Code of Regulations, section 20, permits agencies to incorporate by reference documents under certain conditions. Subdivision (c)(1) of that regulation allows such incorporation when to do otherwise be "cumbersome, unduly expensive, or otherwise impractical" to publish the document in regulatory form. In light of the size and magnitude of the policy and given the burdens associated with translating each of the document's separate provisions into specific regulations, incorporation by reference serves the needs of both efficient use of resources, avoids the cumbersome task of rewriting an entire manual, and avoids the risk of inadvertent disagreement between the regulations and the policies being implemented.

The amendments to this subdivision delete references to specific Program Announcements which are no longer used at CIRM.

Subdivision (b): This section clarifies the specific sections of the policy which are being incorporated by reference, as permitted by Title 1 of the California Code of Regulations, section 20, subdivision (c)(5). Because the unincorporated parts of Section "I" of the policy are informational or background material only, they are not incorporated in the regulation.

The amendment updates the effective date of the policy to refer to the one that embodies these amendments.

DOCUMENT INCORPORATED BY REFERENCE:

CIRM GRANTS ADMINISTRATION POLICY FOR CLINICAL STAGE PROJECTS
VERSION: with a footer that dates the document as "Grants Administration Policy for Clinical Stage Projects - 2015".

SECTION I. GENERAL INFORMATION:

Purpose:

The amendments in this section are technical/nonsubstantive changes to update references and clarify existing language.

SECTION II. GRANT APPLICATION AND REVIEW PROCESS.

Purpose:

Subpart A.

Eligibility: The PI/PD of a For-Profit Organization, or a Non-Profit Organization in existence for less than five years, will be subject to a background check to ensure this individual has not been convicted of fraud or other misuse of funds, nor subject to disbarment of federal funds. There are no citizenship requirements for PIs.

Organizational Eligibility

An applicant organization must be a legal entity that is accountable for both the performance of the approved project or activity and the appropriate expenditure of funds. In general, Non-profit and For-profit research organizations located and conducting research in California are eligible to apply for and to receive CIRM research funding. Under certain programs, CIRM may limit eligibility to meet the specific goals of a Program Announcement (PA) or Request for Applications (RFA). The determination of eligibility includes verification of the applicant's ability to carry out the proposed project and responsibly manage and account for State funds in the organization's accounting systems, and verification of corporate status.

California Organizations (for-profit and non-profit) may use CIRM funds for eligible project costs incurred both in California and outside California. To qualify as a California organization, the organization must have >50% of its employees located in, and paid in, the State of California, and manage the award activities from the California location.

Non-California organizations may also apply; however, CIRM funding can be used only for IND-enabling research activities conducted in California including the costs of services provided

by the Stem Cell Center or for a clinical trial, the cost of manufacturing the product in California and/or the per subject share of the costs of clinical and non-clinical research activities, whether conducted in California or outside of California, that are directly attributable to the treatment of California subjects. The applicant must demonstrate by the application deadline a commitment of funds from other sources for co-funding of allowable project costs, when applicable, as well as support for non-allowable project costs.

Rationale:

The amendments to PI and PD eligibility add scope to the background check requirements to ensure recipients are appropriate stewards for use of state resources. The treatment of for-profit versus non-profit organizations is based on industry experience in terms of risk to funds of misappropriation.

The amendments to Organizational Eligibility clarify existing eligibility requirements to reflect current policy with respect to non-California organizations and the eligible activities that may be funded with CIRM funds. These amendments ensure that research funds are expended in California and that non-California organizations have an incentive to locate and employ labor in California.

Purpose:

Subpart E. Application Review: In accordance with Proposition 71, the Scientific and Medical Research Funding Working Group (Grants Working Group or GWG) makes funding recommendations to the Application Review Subcommittee of the ICOC. The role of the GWG includes consideration of the scientific merit of Applications to support research Facilities. The membership of the GWG consists of seven patient advocate members of the ICOC, 15 scientists from institutions outside of California, and the chairperson of the ICOC (ex officio).

The GWG conducts its review of Applications in accordance with procedures recommended by the GWG and adopted by the ICOC. For each Application, a recommendation on funding is made by the full GWG and submitted to the Application Review Subcommittee of the ICOC, which makes all funding decisions.

Rationale:

The amendments remove the last three paragraphs in “Section II.E. Application Review” that describes clinical application scoring. The current statement is inconsistent with the GWG bylaws, which modified the definition of a Tier 3 score. Given the existing conflict and the potential for future inconsistencies if the Board approves future changes to the GWG bylaws regarding scoring, CIRM is removing this language.

SECTION III. PRE-AWARD AND AWARD.

Subpart C(6)(d)(v). Public Policy Requirements.

Purpose:

This subpart identifies the requirements for documentation for research involving human subjects, and, among other things, requires a copy of the FDA-IND or IDE letter, where applicable when a clinical investigation involves the use of any drugs or devices.

CIRM requires Awardees of CIRM-funded clinical trials to be registered and submit the results of the trial in accordance with FDAAA 801 requirements. These requirements include registering the trial no later than 21 days after the 1st patient is enrolled in the trial and publishing the results no later than 12 months after completion of the trial.

Prior to the issuance of an NOA and during annual Progress Reports (see chapter V, section O, *Reporting Requirements*), an Awardee shall certify to CIRM that any IRB approval required to conduct the CIRM-Funded Project or Activity is obtained or will be obtained before CIRM funding is spent on such activities. (see section D, *Just-in-Time Policy*). CIRM will not authorize continued funding of active Awards without current certification for Human Subjects research.

Rationale:

The amendments CIRM add a requirement for all CIRM-funded clinical trials to be registered and submit the results of the trial in accordance with FDAAA 801 requirements. These requirements include registering the trial no later than 21 days after the 1st patient is enrolled in the trial and publishing the results no later than 12 months after completion of the trial. The amendments ensure timely conduct of the trial and sharing of the results of publicly financed clinical trials.

SECTION IV. AWARD ACCEPTANCE AND TERMS.

Subsection B(1). Terms: Meetings:

Purpose:
As amended this subpart provides that CIRM has the right to obtain communications to or from the FDA and any other similar non-US regulatory bodies regarding the CIRM-funded project. CIRM also has the right to attend key FDA meetings regarding the funded project, including but not limited to any clinical milestone meeting, Regenerative Advance Therapy designation meetings, or clinical hold meeting (FDA Meetings). To facilitate CIRM's participation in such meetings, Awardee shall notify CIRM as soon as practicable after it has scheduled an FDA meeting and provide to CIRM any data package(s) or other information, including confidential and/or proprietary information, prior to submission to the FDA as well as any FDA Meeting minutes. CIRM reserves the right to share such information with CIRM's confidential advisers.

Rationale:

The amendments clarify the types of communications CIRM has the right to obtain, including in the context of communications from foreign regulatory bodies. Access to these communications and meetings ensure CIRM has visibility into the risks associated with a given CIRM-funded trial and ensures CIRM is able to make informed decisions regarding ongoing funding of trials.

Subsection C. Award Conversion

Purpose:
Under this section, recipients of CIRM's Clinical Stage Program awards have the option to treat their awards as loans within the earlier of the submission of an application for marketing approval by the Food and Drug Administration or seven years from the effective date of the award. Unless the parties agreed to different terms, the awardee would be required to repay the loan balance within ten days of making the loan election at a rate that would escalate based on the date of repayment. The loan election would become final only after the awardee has satisfied the terms of the election. If an awardee does not make this election, its award would be treated as a grant.

Rationale:
The amendments make nonsubstantive changes to eliminate reference to non-existent funding opportunities and propose optional language to the payback formula. Revisions to the payback formula attempt to strike the proper balance between risk and return.

SECTION V. PAYMENT AND USE OF FUNDS.

D & E. Allowable Project Costs and Activities; Unallowable Project Costs and Activities:

Purpose:

The amendments to allowable activities are amended to include insurance that is deemed necessary and specific to the project not otherwise covered by Facilities or Indirect costs, including clinical trial insurance and medical liability (malpractice) insurance when the project involves human subjects.

The amendments to unallowable activities add the following:

- Legal costs incurred in defending or prosecuting claims, whether equitable or monetary.
- Intellectual property costs including, but not limited to, invention, copyright, patent, licensing or royalty costs, filing fees, translation costs, examination fees, annuity costs and grant fees, and related attorney's fees.
- Routine, patient standard of care costs or any cost of care covered by a 3rd party provider.

Rationale:

The proposed amendments align the types of direct project costs that may or may not be supported with that of the NIH Grants Policy Statement. This highlights the areas of common

interest to our awardees and ensures consistency in application of commonly accepted administration rules and accounting.

K.4 – Change in California Organization Eligibility

Purpose:

This section adds to the list of items require prior CIRM approval when a California-based Organization becomes a Non-California-based Organization given this change determines the scope of allowable project costs and will require a reduction to the remaining award amount. If a California-based Organization becomes a Non-California-based organization, CIRM will required the remainder of the award to be reduced effective the date of the organization's status change to cover only the allowable project costs available to Non-California-based Organizations. If a Non-California-based Organization becomes a California-based Organization, CIRM requires the existing award amount as approved by the ICOC to be maintained, but to Allow the Awardee to reallocate the remaining funds to also cover any additional allowable project costs available to California-based Organizations.

Rationale:

CIRM proposes to add a requirement for a CIRM-funded Awardee to immediately report whether their organization's status as a California-based or Non-California-based organization has changed in light of the fact that such status will determine the scope of allowable project costs.

If a California-based Organization becomes a Non-California-based organization, we will propose to reduce the remainder of the award effective the date the organization's status changed to only cover the allowable project costs available to Non-California-based organizations. If a Non-California-based organization becomes a California-based organization, we propose to maintain the existing award amount as approved by the ICOC but allow the Awardee to reallocate remaining funds to also cover any additional allowable project costs available to California-based organizations.

Q. Failure of Compliance and Award Termination

Purpose:

This section states the potential range of consequences if an Awardee or PI violates conditions and terms of the Award and other deficiencies. The language is amended to include circumstances where the Awardee and/or the Award become ineligible based on the criteria specified in the program announcement.

Rationale:

This addition is necessary to address circumstances where a program fails to meet eligibility after an Award has been made. This is necessary to enforce the requirement that a program maintain its eligibility for funding under the CIRM program.

SPECIFIC PURPOSE OF REGULATION AND FACTUAL BASIS FOR AMENDMENTS TO REGULATION:

The Grants Administration Policy for Clinical Stage Projects is required for effective grants management by CIRM. Further, this GAP is necessary for meeting the specific reporting requirements of the California State Legislature and also for disseminating the outcomes of funded research to interested constituencies and the general public. The GAP outlines statutory requirements applicable to CIRM and its working groups and those governing CIRM-funded research. The Policy also serves to guide award recipients on their responsibilities as CIRM Awardees. Principal investigators, Program Directors, and Organizational Officials with award management responsibilities may refer to pertinent sections for answers to questions that arise concerning the administration of the awards and compliance protocols. The GAP is necessary to achieve the requirements and purposes discussed above.

TECHNICAL, THEORETICAL, AND/OR EMPIRICAL STUDY, REPORTS, OR DOCUMENTS:

A. Documents or Laws:

1) Section 801 of the Food and Drug Administration Amendments Act of 2007, known as FDAAA 801

B. Public Input:

None.

Copies of the documents referenced above are available at the offices of CIRM located at 1999 Harrison Street, #1650, Oakland, California, 94612. Alternatively, transcripts and agendas for public meetings identified above are available on CIRM's website, www.cirm.ca.gov.

MANDATE FOR SPECIFIC TECHONOLOGIES OR EQUIPMENT:

The proposed regulation does not mandate the use of specific technologies or equipment.

REASONABLE ALTERNATIVES TO THE PROPOSED AMENDMENTS AND THE AGENCY'S REASONS FOR REJECTING THOSE ALTERNATIVES:

In view of information currently possessed, no reasonable alternative considered would be more effective in carrying out the purposes for which the regulation is proposed or would be as effective as the regulation.

CIRM invites interested persons to present statements or arguments with respect to alternatives to the proposed action at the scheduled hearing or during the written comment period.

REASONABLE ALTERNATIVES TO THE PROPOSED AMENDMENTS AND THAT WOULD LESSON ANY ADVERSE IMPACT ON SMALL BUSINESS:

CIRM has made the initial determination that the proposed action will not have an adverse impact on small business. The GAP applies to CIRM Awardees who receive funds from CIRM to perform research. As such, no private conduct or commercial activity by a business of any size is being regulated.

EVIDENCE SUPPORTING FINDING OF NO SIGNIFICANT STATEWIDE ADVERSE ECONOMIC IMPACT DIRECTLY AFFECTING BUSINESS:

CIRM has made the initial determination that the proposed action will not have a statewide adverse economic impact. This action is not expected to have a direct impact on the creation or elimination of jobs, nor the creation of new businesses or elimination of existing businesses, nor the expansion of business currently doing business within the State of California because the amendments affect only administrative requirements regarding use of grant funds. The use of grant funds is required neither by law nor these regulations. To the extent the regulation facilitates use of the funds and encourage development of intellectual property and return to the state as required by law, and to the extent California institutions apply for and receive research funds, such requirements are indirectly attributable to increased economic activity spurred by the investment research funds in the state and resultant positive business and employment development. Also, to the extent the policy makes it possible for the expenditure of research funds in the state, and to the extent that research results in medical treatments and cures for chronic disease and injury, the policy indirectly benefit the health and welfare of California residents who will benefit from such treatments and cures.

ECONOMIC IMPACT ANALYSIS REQUIRED BY GOVERNMENT CODE SECTION 11346.3, SUBDIVISION (b)

Economic Impact Assessment Per Government Code Section 11346.3, subdivision (b):

For adoption of CIRM Grants Administration Policy for Clinical Stage Programs

Action: The regulatory action enacts the CIRM grants administration policy that is applicable to Clinical Stage Programs (section 100503 and document incorporated thereby). The regulation states the requirements attendant to applying for, receiving and expending CIRM research funds. The action does not regulate a commercial or private activity of any individual or institution but reaches only administrative functions of institutions in connection with the use of CIRM research funds.

Impact:

Under section 3 of the "California Stem Cell Research and Cures Act," which established the California Institute for Regenerative Medicine, funds for this agency are continuously appropriated without regard to fiscal year and not subject to budgetary control. By statute, this agency requires strict fiscal and public accountability through mandatory independent audits.

CIRM has determined that that proposed regulatory action has no impact on small businesses. The regulation implements conditions on awarding grants for stem cell research. This research will be conducted almost exclusively by large public and private non-profit institutions, as well as large for-profit institutions. As such, and the regulations are not expected to adversely impact small business as defined in Government Code section 11343.610. Application for grant funds is voluntary and grant awards are required by Proposition 71 to include a prescribed additional amount to cover any costs associated with administration of the grant by grant recipients.

This action is not expected to have a direct impact on the creation or elimination of jobs, nor the creation of new businesses or elimination of existing businesses, nor the expansion of business currently doing business within the State of California because the regulation affect only administrative requirements regarding use of grant funds. The use of grant funds is required neither by law nor these regulations. To the extent the regulations facilitate use of the funds and encourage development of intellectual property and return to the state as required by law, and to the extent California institutions apply for and receive research funds, such requirements are indirectly attributable to increased economic activity spurred by the investment research funds in the state and resultant positive business and employment development. Also, to the extent the regulation makes it possible for the expenditure of research funds in the state, and to the extent that research results in medical treatments and cures for chronic disease and injury, the regulation indirectly benefit the health and welfare of California residents who will benefit from such treatments and cures.