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CLIN4: Funding Opportunity for Late-Stage Development Projects

PROGRAM ANNOUNCEMENT
03.12.24

CLIN4: Funding Opportunity for Late-Stage Development Projects

Objective

The mission of California Institute for Regenerative Medicine (CIRM) is to accelerate world class science to deliver transformative regenerative medicine treatments in an equitable manner to a diverse California and world.

The objective of this funding opportunity is to support supplemental activities associated with an active CIRM-funded CLIN2 project that if successful, will enable a sponsor to achieve readiness to apply for marketing approval and to initiate essential pre-commercial activities for the investigational therapy that is the subject of the active CLIN2 award.

Under this program, CIRM will act not only as a funding agency, but will also devote significant internal resources and leverage its external team of world-class subject matter experts to actively advance the project. The result of a successful application will be the formation of a true partnership that both accelerates the program and gives it the greatest opportunity for success.

Contact

For information about this program announcement send email correspondence to Clinical@cirm.ca.gov.

Award Information

What activities will CIRM fund?

CIRM funds may be used to support the following activities under this opportunity:

- Late-stage product development activities including but not limited to:
  - Activities necessary for filing a Biologics License Application (BLA) with the FDA, such as conduct of a Pre-BLA meeting with the FDA or compilation of an electronic common technical document (eCTD)
  - Commercial development activities such as pharmacoeconomic analysis, budget impact models (managed health-payer perspective)
  - Initiation of pre-commercialization activities such as production of a Payers' cost-effectiveness analysis report, compilation of an AMCP (Academy of Managed Care Pharmacy) Dossier
  - Development of a supply chain strategy
- Product manufacturing activities necessary to submit a BLA and obtain marketing approval, including gap analysis of the commercial manufacturing process.
- Clinical research and non-clinical research activities that are required by the FDA for BLA readiness.
- Non-trial clinical activities (comparability studies, data compilation, etc.) that are necessary to achieve BLA readiness.
- Compassionate use of the investigational therapy for a maximum of 3 patients in the period after close of enrollment and prior to marketing approval. Compassionate use requests must have FDA approval and agreement with the drug product supplier and must be in conjunction with BLA activities noted above.
- Activities that incorporate principles of diversity, equity and inclusion (DEI) into the development and delivery of the therapeutic.

CIRM funds **cannot** be used to support the following activities under this opportunity:

- ✘ Specific activities already funded under the parent CLIN2 award
- ✘ Activities not necessary to obtain FDA marketing approval
- ✘ Activities occurring after attaining marketing approval
- ✘ Studies for therapeutic candidate discovery including lead optimization or lead candidate selection
- ✘ Preclinical IND-enabling activities
- ✘ Studies to remove a clinical hold by the FDA

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What is the award amount and duration?

The proposed Project Period must not exceed 48 months from the award start date, approximately 45 days after the date of ICOC approval. During the Project Period, CIRM funds shall only be used for allowable project costs and activities.

Total CIRM-Funded Project Costs for a CLIN4 project are limited to $12,000,000 per award.

The amount of total project costs requested must be adequately justified and is subject to adjustments prior to issuance of an award based upon assessments of the Grants Working Group (GWG), the CIRM team, or by the Application Review Subcommittee of CIRM's Governing Board.

How will funds be awarded?

Funds will be disbursed pursuant to a CIRM Notice of Award. Awardees may elect, upon completion of their award, to treat their award as a loan pursuant to CIRM's award conversion policy. (See the most recent Grants Administration Policy for Clinical Programs.) Except for the first payment issued upon initiation of an award, payments will be disbursed upon completion of specific operational milestones. Continued funding is contingent upon timely progress, as outlined in the operational milestones established under the Notice of Award, and, when applicable, the ongoing ability of the applicant to fund its operations and to satisfy its co-funding commitment.

Costs resulting from a delay or failure to meet an Operational Milestone will be the sole responsibility of the recipient. Successful applicants will have thoughtfully accounted for foreseeable project risks and developed contingency plans that ***do not*** involve additional funding from CIRM (see "Plans for Risk Mitigation & Financial Contingency" under application components). CIRM expects projects under this program to advance rapidly through clinical development; hence, CIRM does not allow applicants to propose more than 48 months of CIRM funding.

Eligibility

What types of projects are eligible for funding?

To be eligible, the proposed project must satisfy the following requirements (1-11):

(1) The applicant must be ready to initiate work on the funded project within 45 days of approval.

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded project within 45 days of approval and authorization for funding by the Application Review Subcommittee of CIRM's governing board, the Independent Citizens' Oversight Committee ("ICOC").

Because of the open and ongoing nature of this Program Announcement, investigators should only apply when their project has reached the stage where all eligibility criteria are met. **CIRM reserves the right to refuse to consider an application that is submitted prior to the completion of all necessary prerequisites.**

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(2) The applicant must have an active CLIN2 award.

Applicants for a CLIN4 award must have an active CLIN2 award supporting the completion of a clinical trial (phase 1/2, 2, or 3) for an investigational therapy.

(3) The applicant must have completed 50% of the milestones of their active CLIN2 award.

Applicants must have completed at least 50% of the milestones on their CLIN2 parent project that this CLIN4 award will supplement.

(4) The applicant must have completed an End-of-Phase 2 meeting or equivalent with the FDA.

Applicants must have completed an End-of-Phase 2 meeting or equivalent with the FDA and have concurrence on requirements for a BLA filing for the investigational therapy that is the subject of the active CLIN2 award.

The applicant must present correspondence with the Food and Drug Administration confirming that the combined activities being conducted under the associated active CLIN2 award and this supplemental CLIN4 award, if successful, could support a BLA filing and a potential marketing approval decision.

(5) The applicant must commit appropriate co-funding and demonstrate availability of funds.

CIRM will require co-funding from the for-profit applicant or for-profit partner of the non-profit applicant based on the total "Allowable Project Costs". Non-profit applicants may provide co-funding, but it is only required when project costs are in excess of the maximum CIRM award amount.

Allowable Project Costs are those costs permitted under CIRM policies and regulations and include direct, facilities and indirect costs. The sum of CIRM funds requested plus the co-funding contribution by the applicant make up the total Allowable Project Costs. For- profit CLIN4 applicants must commit at least 40% of total Allowable Project Costs as the co-funding amount on the project. Only funds that will be spent concurrently with CIRM funds (i.e., no sooner than board approval and no later than completion of the final Operational Milestone) will qualify toward this co-funding requirement.

Description and documentation demonstrating the commitment of funds to cover the proposed co-funding amount must be provided at the time of application submission by the application deadline. The co-funding may come from any funding source arranged by the applicant but may not include "in-kind" or similar types of support. The applicant may propose to use cash-on-hand, committed funding and/or planned fundraising as sources of funds for the co-funding commitment but must demonstrate that it will have cash-on-hand at project start date to co-fund at least the first operational milestone disbursement. Applicants are advised to refer to the Solvency & Co-Funding Template in the Document Uploads Section of the Application for additional instructions and guidance on co-funding requirements.

Alternatively, for-profit applicants and for-profit partners of non-profit applicants may elect to fulfill all or a portion of the minimum co-funding requirement by agreeing to

issue equity warrants to CIRM. Applicants electing the warrant-based co-funding requirement may request CIRM funding to cover the co-funding commitment up to the award limit. Applicants who elect the warrant-based co-funding requirement must sign the Warrant Term Sheet at application submission and must issue equity warrants at the award start date. Applicants are advised to contact bd@cirm.ca.gov for additional guidance and information on warrant-based co-funding.

(6) For-profit organizations must demonstrate solvency.

For-profit organizations must provide documentation that shows cash on hand or funding from committed sources that will cover company expenses for 180 days from the date of application submission. These funds must be distinct from, and in addition to, funds for meeting the co-funding requirement for the term of the project and funds for the applicant's financial contingency plan. The determination of solvency will be made at CIRM's sole discretion.

(7) There is a limit of one CLIN4 award per parent CLIN2 award.

Applicants are only eligible for a single CLIN4 award per parent CLIN2 award.

(8) The application must be accurate and complete.

All required components of the application must be completed and may not contain false or inaccurate information.

(9) The applicant must be in "good standing".

Applicants must certify that they are in good standing, as follows:

- The applicant's Chief Executive Officer, Chief Financial Officer, and Principal Investigator must not have been convicted of, or currently under investigation for, crimes involving fraud/misappropriation;
- The applicant must have accounting systems in place that are capable of tracking CIRM funds; and
- The Principal Investigator or key personnel named in the application must not be currently under investigation for research misconduct by the applicant institution or a funding agency and must not be currently debarred by HHS Office of Research Integrity.

Who can apply?

Only CIRM grantees with an active CIRM-funded CLIN2 award can apply.

California Organizations

A California Organization is a for-profit or non-profit organization that employs and pays more than 50% of its employees in California, and that directs and controls the award activities from the California location.

For a California Organization, Allowable Project Costs include:

- ✓ Costs for manufacturing activities that are necessary to achieve BLA readiness;

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- ✓ Costs for clinical research and non-clinical research activities that are required by the FDA for BLA readiness;
- ✓ Costs for non-trial clinical activities (comparability studies, data compilation, etc.) that are necessary to achieve BLA readiness;
- ✓ Costs for late-stage product development/pre-commercialization activities;
- ✓ Costs of activities to support principles of DEI in the development and delivery of the therapeutic; and
- ✓ The per patient share of costs for compassionate use of the therapy in the period after close of enrollment and prior to marketing approval.

Non-California Organizations

A Non-California Organization is a for-profit or non-profit organization that employs and pays 50% or less of its employees in California.

For a Non-California Organization, Allowable Project Costs include:

- ✓ Costs for manufacturing activities wholly conducted in California that are directly attributable to the submission of a BLA;
- ✓ Costs for clinical research and non-clinical research activities wholly conducted in California that are required by the FDA for BLA readiness;
- ✓ Costs for non-trial clinical activities (comparability studies, data compilation, etc.) wholly conducted in California that are directly attributable to the filing of a BLA;
- ✓ Costs for late-stage product development activities wholly conducted in California that are directly attributable to the filing of a BLA; and
- ✓ Costs of activities wholly conducted in California to support principles of DEI in the development and delivery of the therapeutic.

Unallowable Costs

Unallowable Project Costs include:

- ✗ The costs of activities performed by a separate out-of-state organization that retains intellectual property or independent publication rights in any intellectual property (e.g., invention, technology, data) arising out of the CIRM funded project.
- ✗ Project costs incurred before the date the ICOC approves the application for funding, which can be as early as 90 days post application submission.
- ✗ The costs of any activity that is not required for BLA submission.

CIRM Discretion

CIRM may determine, in its sole discretion, whether an applicant is a California organization and whether the project activities are allowable. If an applicant is a non-

California organization at the time of application, but intends to become a California organization by the time this project would need to execute a CIRM award contract (~115 days from time of application), then the applicant may submit a budget that includes the Allowable Project Costs for California organizations and must describe their intentions and the timing of becoming a California organization in this application.

Funding of Non-Allowable Project Activities

The applicant must demonstrate by the application deadline a commitment of funds from other sources for non-allowable project activities that are necessary to achieve the goals of the application.

Who can serve as the Principal Investigator (PI)?

To be eligible, the PI must satisfy the following requirements:

- Must be an employee of the applicant organization or be accountable for the conduct of the proposed project to the applicant organization through a formal contract.
- Must propose a level of effort on the project consistent with achieving the project's aims and not less than 15% on average over the project period. (Note: "project" includes both the CIRM-funded and applicant co-funded components.) Any effort for which salary from CIRM is claimed must be expended in California.
- Must be authorized by the applicant organization to conduct the research and assume the responsibilities of the PI.
- Must not currently have another application pending review or approval under this funding opportunity.
- Must not currently have another application that is substantially similar or has overlapping activities pending review or approval under any CIRM opportunity.

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Application Review Information

Schedule and Deadlines

Applications Due	2:00 pm (PDT/PST) on the last business day of each month (except October)
Grants Working Group (GWG) Review	Approximately 60 days post submission
ICOC Review and Approval	Approximately 90 days post submission
Award Start	Must start within 45 days of award approval (i.e., approximately 135 days post submission)

What is the process for evaluating an application?

Pre-submission Consultation

In accordance with CIRM's mission, the Agency is committed to helping develop promising stem cell treatments by partnering with world-class investigators. Therefore, prospective applicants with an active CLIN2 award are encouraged to contact CIRM before applying with questions or to discuss their project's eligibility, scientific, or budget considerations.

Eligibility Review

CIRM will assess whether the proposed project meets eligibility requirements sought under this program. If CIRM determines, in its sole discretion, that an application does not meet the eligibility requirements of the program, CIRM will notify the applicant of its decision, and if CIRM deems it appropriate allow an opportunity to remedy. If CIRM deems it inappropriate, or if the applicant does not remedy the error in a timely manner, CIRM will terminate all further action on the application.

CIRM may exercise its authority to make eligibility determinations at any time before an award is executed.

Budget Review

CIRM will review the proposed budget to assess how well the proposed costs are justified and confirm that costs designated as Allowable Project Costs comply with CIRM policies. When a proposed budget is not well justified or does not comply with Allowable Project Cost policy, adjustments to the budget will be required by CIRM prior to further review of the application, at CIRM's sole discretion. Applicants will be notified of the specific discrepancies and applications will not be forwarded for scientific review until an amended budget has been submitted and approved by CIRM. Additionally, project budgets may be subject to further adjustments prior to

issuance of an award based upon assessments of the GWG, the CIRM team, or by the Application Review Subcommittee of the ICOC.

Scientific Review

The scientific merit of each application will be assessed by the GWG, which is composed of fifteen subject matter experts from outside California, seven patient advocate and nurse members of the ICOC, and the Chair of the ICOC. The list of scientific members who may participate in the GWG review can be found at http://www.cirm.ca.gov/WorkingGroup_GrantsReview. The composition of the ICOC can be viewed at https://www.cirm.ca.gov/board-and-meetings/board/.

The fifteen participating scientists and clinicians on the GWG will evaluate the applications and score them according to scientific and technical merit, applying the review criteria described below. The GWG will score each application and make one of the following specific recommendations to the ICOC's Application Review Subcommittee: 1) fund the project based on its exceptional merit; 2) do not fund the project but allow for resubmission to address areas for improvement; or 3) do not fund the project and do not allow resubmission for six months. In the event the GWG recommends amendment and resubmission, the applicant may elect, prior to the ICOC's final funding decision, to amend and resubmit the application for reevaluation by the GWG.

The ICOC patient advocate and nurse members participating on the GWG will evaluate the applications on diversity, equity, and inclusion.

The ICOC's Application Review Subcommittee will make final funding decisions giving consideration to the GWG recommendations and any CIRM team recommendations.

Consideration of Related CIRM Award Information (If Applicable)

The GWG may consider information from a previously funded and related CIRM award as part of its review. CIRM will provide the GWG with objective information regarding a related award that CIRM, in its sole discretion, deems relevant, including but not limited to achievement of specific milestones, data, and outcomes for a related CIRM award or awards.

A "related CIRM award" includes: (1) an award for which the applicant PI served as the PI, a co-PI, a co-investigator, or otherwise substantially participated in the conduct of the award; (2) an award involving the same research project or product; or (3) an award that includes overlapping team members.

Confidentiality

CIRM's confidentiality and conflict screening rules apply to everyone who will have access to applications or who will attend any review meeting in which confidential information is discussed, including but not limited to CIRM team members, reviewers and members of the ICOC. (Per Gov. Code §6254.5(e) non-public records may be disclosed to government agencies under confidentiality agreements).

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How will the scientific merit of an application be evaluated?

Scientific members of the GWG will evaluate and score applications based on the following five review criteria:

1. Does the project hold the necessary significance and potential for impact?

Given any changes that may have occurred since submission of the parent CLIN2 application, is the therapeutic approach likely to provide an improvement over the standard of care for the intended patient population in the current therapeutic landscape? Does the proposed treatment continue to offer a sufficient value proposition such that the value created by the treatment supports its adoption by patients and/or health care providers?

2. Is the rationale sound?

Has agreement been reached with FDA regarding what is needed to achieve BLA readiness for the therapeutic approach in the target indication? Have major specific questions and concerns raised in discussions between the sponsor and FDA been resolved? Could the totality of the safety and efficacy data from the current and prior trials support a successful BLA filing?

3. Is the project well planned and designed?

Is the project appropriately designed to achieve readiness for a BLA filing for the therapeutic candidate and is the proposed BLA plan consistent with what has been discussed and agreed upon with the FDA? Is the proposed plan for manufacturing commercial-grade product appropriately designed? Are all proposed activities necessary to achieve readiness for BLA filing, and does the timeline demonstrate an urgency that is commensurate with CIRM's mission?

4. Is the project feasible?

Are the intended objectives likely to be achieved within the proposed timeline? Is the proposed team appropriately qualified and staffed? Does the team have access to all the necessary resources to conduct the proposed activities, including commercial grade manufacturing? Does the team have a viable contingency plan to manage risks and delays?

5. Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?

Has the applicant adequately considered the influence of race, ethnicity, sex, gender, and age diversity in the development of the proposed therapy?

Application Components and Submission

How does one apply?

Applications must be created, completed, and submitted online using the CIRM Grants Management Portal at https://grants.cirm.ca.gov. Any prospective PI must create a login in the system to access application materials and apply. Applications are available in the system only to the PI and his or her designee. A PI may submit only a single application in a given review cycle. The Grants Management Portal

provides instructions for completing all the necessary components and submitting a final application.

Applications are due by 2:00pm (Pacific Time) on the last business day of each month (except October). Applications received after the deadline will be deferred to the next monthly review cycle.

What components does an application include?

CIRM's online application is designed to collect information for CIRM staff to assess eligibility, for Grants Working Group reviewers to evaluate the project, and for CIRM to rapidly initiate an award if the project is approved for funding.

It includes overview sections characterizing the proposed team, the proposed product, and major planned activities; an eligibility form; a template proposal; a detailed Activity-Based Budget, and an uploads section for reference documentation including Key Personnel Biosketches, FDA Correspondence and Manufacturing Plan.

What are the contents of the proposal?

CLIN4 applications must describe activities proposed to achieve BLA readiness for the therapeutic being developed under the parent CLIN2 as agreed to with the FDA. CLIN4 applications that reprise the parent CLIN2 proposal will be deemed ineligible by CIRM.

Project Summary: High-level summary of the proposed CLIN4 project.

Target Product Profile: Updated template-based product label containing base case and optimal product specifications for the proposed product, reflecting any new information obtained since submission of the parent CLIN2 application.

Value Proposition: Description of any new information or change relevant to the unmet need, therapeutic landscape, or standard of care since submission of the parent CLIN2 application. Discussion of any potential impact to the value proposition for the therapeutic candidate.

Diversity, Equity, and Inclusion (DEI): A statement describing how the research team has considered the influence of race, ethnicity, sex, gender, and age diversity in the development of the proposed therapy.

Scientific Rationale: Summary of enrollment demographics and any available safety and efficacy data. Summary of regulatory interactions since the start of the CLIN2 award with emphasis on End-Of-Phase 2 or equivalent meeting(s) with FDA. Summary of specific issues and concerns discussed with FDA regarding a potential BLA filing and agreements reached. Summary of sponsor's understanding of FDA expectations regarding a BLA filing.

BLA Readiness Plan: Summary of all activities necessary to achieve readiness for a BLA filing, including activities being conducted under the parent CLIN2 award, activities proposed under this CLIN4 award, or any activities supported by other funding sources.

Gantt-Like Timeline: Timeline for all activities necessary to achieve readiness for a BLA filing with specific activities proposed under this CLIN4 award identified and/or highlighted.

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CLIN4 Project Plan: Detailed description of the activities proposed under the CLIN4 award, describing why they are necessary to achieve readiness for a BLA filing and how they will be implemented.

Commercial Manufacturing Plan Synopsis: Description of the plan to manufacture commercial-grade product, including gap analysis of the process for commercial manufacturing. Template-based synopsis describing key aspects of the plan to manufacture commercial-grade product, including a description of the facility where product is/will be manufactured. Status summary of validation of important processes and assays involved in the manufacture of the candidate therapeutic.

Plans for Risk Mitigation & Financial Contingency: Project risks, surveillance and mitigation strategies, associated costs, and non-CIRM sources of contingency funding.

Team Organization: Qualifications of the proposed team and plans for team collaboration.

Resources & Project Environment: Institutional offerings that will benefit the project.

Commercial Development: Plans for effective commercial development of the product.

References

How does one address diversity, equity, and inclusion (DEI)?

All applicants for the CLIN4 program will be required to provide a statement describing how the research team has considered the influence of race, ethnicity, sex, gender, and age diversity in the development of the proposed therapy. Applicants should discuss the limitations, advantages and/or challenges of developing a product that addresses the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. Applicants should also address how the research team has or will incorporate diverse and inclusive perspectives and experience in the implementation of the research project, including, for example, developing partnerships with patient organizations, acquiring training in cultural competence and/or DEI, utilizing institutional resources for DEI, and allocating funds and/or personnel to address DEI.

The GWG and CIRM's governing board will evaluate these statements as a review criterion in making funding recommendations. Priority will be given to projects with the highest quality plans in this regard.

Who are Key Personnel?

In the application, we ask you to identify by name pertinent Key Personnel and their specific roles on the project. Key Personnel are defined as (1) the principal investigator or program director; or (2) any other person, including an independent consultant or an employee of a Subcontractor or Partner, who is expected to contribute to the scientific development or execution of the project in a substantive, measurable way *and* who is expected to: (a) receive or has been promised income, or anything else of value, of $10,000 or more per year for his or her contribution to the project or (b) contribute one percent (1%) or more effort to the proposed project.

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"Key Personnel" does not include a person who is expected to be involved in the proposed project but who does not satisfy conditions (1) or (2).

Individuals who do not meet the definition of Key Personnel may be supported with CIRM funds, but should **not** be identified by name in the application. Such unnamed personnel may be referenced indirectly by their role on the project (e.g., technician). The budget includes a line item for requesting support for unnamed personnel.

What should one know before preparing the budget?

A specific and well-justified activities-based budget must be provided that clearly outlines the total costs of the project, including those costs not proposed to be funded by CIRM. The corresponding budget justification should provide enough detail to allow budget professionals to determine the appropriateness of the costs in relation to the activities being performed. Allowable Project Costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy for Clinical Stage Projects (https://www.cirm.ca.gov/sites/default/files/files/funding_page/CIRM_Grants_Administration_Policy_for_Clinical_Stage_Projects.pdf). Generally, project costs for personnel, supplies, travel, equipment, and subcontracts may be claimed. Limits for specific cost categories must be observed.

What are Direct Facilities costs and how much can an applicant claim?

Direct Facilities Costs are the general operating costs of the Awardee's facilities attributable to housing all elements of the CIRM-funded project or activity. Facilities costs for non-profit applicant organizations are limited to the current applicable, federally negotiated rates for the organization as defined by the Office of Management and Budget (OMB) Circular A-21 or A-122. Facilities rates for for-profit applicant organizations are limited to 35% of the direct project costs. Facilities rates are applied to direct project costs exclusive of the costs of equipment, tuition and fees, research patient care costs, as well as the costs of each individual subcontract, consultant, and service agreement in excess of $25,000. The facilities cost rates approved and in place at the time of the application are to be applied to the entire award project period.

What are indirect costs and how much can an applicant claim?

Indirect Costs are administrative costs of the awardee incurred for common or joint objectives, which cannot be readily and specifically identified with a particular project. For-profit organizations cannot claim indirect (administrative) overhead costs. For non-profit organizations, indirect costs will be limited to 20% of allowable direct research funding costs awarded by CIRM (i.e., direct project costs and facilities costs), exclusive of the costs of equipment, tuition and fees, research patient care costs, as well as the costs of each individual subcontract, consultant, and service agreement in excess of $25,000. The indirect cost rate budgeted at the time of application is to be applied to the entire award project period.

How does one utilize CIRM Infrastructure Programs?

CIRM has established Infrastructure Programs to help CIRM applicants and Awardees prepare competitive applications and to accelerate the conduct of high quality stem cell clinical trials and research.

The CIRM Alpha Stem Cell Clinics are a statewide Network composed of 10 leading California Medical Centers (https://www.cirm.ca.gov/patients/alpha-clinics-network). The Network has performed over 200 stem cell clinical trials for academic and commercial partners (https://www.cirm.ca.gov/patients/alpha-clinics-network/alpha-clinics-trials). Applicants and awardees can partner with the Alpha Stem Cell Clinics Network to identify California trial sites, evaluate trial participant cohorts, and accelerate trial initiation and completion.

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Award Administration

Issuance of Award

A CIRM award is issued via a Notice of Award Agreement, which is the formal contract that defines the terms and conditions of an award and documents the commitment of funds from CIRM.

Operational Milestones and Payment

CIRM funds under the award will be disbursed based on achievement of specific Operational Milestones established by CIRM. An "Operational Milestone" is an objective event that is indicative of project progress occurring as proposed in the application. CIRM establishes Operational Milestones for inclusion in the Grant or Loan Agreement based upon information provided in the Application. Upon issuance of the award, funds budgeted to achieve the initial Operational Milestone will be disbursed. Upon the successful completion of the initial Operational Milestone and each successive milestone, additional funds will be disbursed. If funds allocated to a specific Operational Milestone (including both CIRM funds and the required applicant co-funds) are exhausted prior to achievement of that milestone, the Awardee will be responsible for covering any remaining costs. CIRM expects that the applicant's contingency plan will identify project timeline and budget risks and will provide details for covering such costs, including the source of funding. CIRM reserves the right to make adjustments to the timeline for inclusion in the Notice of Award to ensure that funds are appropriately dispersed across Operational Milestones.

If CIRM determines, in its sole discretion, that an awardee has failed to satisfy an Operational Milestone within four months of the date that the Operational Milestone was scheduled to have been completed, or if the delay is not addressed to CIRM's satisfaction, CIRM may permanently cease disbursements and terminate the award.

Suspension Events

CIRM reserves the right to hold or terminate disbursements if CIRM determines, in its sole discretion, that a Suspension Event has occurred. A "Suspension Event" means a pre-defined condition that triggers a hold of CIRM funding until the suspension event has been resolved, if resolvable. Following a Suspension Event, the Awardee is expected to provide CIRM with a plan to resolve the issue that triggered the Suspension Event. CIRM establishes Suspension Events for inclusion in the Notice of Award based on information provided in the Application.

Reporting

Awardees will be required to provide periodic written progress and financial reports to CIRM. CIRM requires awardees enrolling trial participants in the course of the award to provide participant demographic data as well as other reporting requests including and not limited to race, ethnicity, gender, age, sexual minority status, income bracket, and medical insurance status.

Upon approval of an award, CIRM may assemble a Market Approval Advisory Panel (MAAP) to partner with the Awardee. The MAAP will be composed of at least one CIRM science officer, one external advisor, and a patient representative and will

provide guidance and advice to foster success of the project. MAAPs have the ability to enlist the help of CIRM's external subject matter experts when needed.

Failure to co-operate with CIRM staff or the MAAP for information requests related to the Award, including FDA documentation and minutes, may lead to a Suspension Event or other CIRM remedies, including termination of the Award.

CIRM Regulations

Grant or Loan awards made through this program announcement will be subject to all applicable CIRM regulations. These regulations can be found on CIRM's website at https://www.cirm.ca.gov/our-funding/cirm-stem-cell-grant-regulations/

Clinical Trials

Clinical trials funded by CIRM must be listed on http://www.clinicaltrials.gov/ and awardees must submit the administrative and scientific results of the trial to the clinicaltrials.gov results database within one year of completion of the studies (in compliance with FDAAA801), for the benefit of the field.

Change in Status

Applicants are required to notify CIRM of any material change in status while the application is pending review, e.g., the applicant has commenced the trial that is the subject of the award, the applicant no longer qualifies as a California Organization, etc.

A list of frequently asked questions regarding managing a CIRM award can be found at https://www.cirm.ca.gov/researchers/managing-your-grant

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Definitions

"California organization" means: An entity, regardless of profit status, that has >50% of its employees located in, and paid in, the state of California, and that directs and controls the award activities from the California location.

"For-profit organization" means: a sole-proprietorship, partnership, limited liability company, corporation, or other legal entity that is organized or operated for the profit or financial benefit of its shareholders or other owners. Such organizations also are referred to as "commercial organizations".

"Non-profit organization" means: (1) a governmental entity of the state of California; or (2) a legal entity that is tax exempt under Internal Revenue Code section 501(c)(3) and California Revenue and Taxation Code section 23701d.

"Operational Milestone" means an objective event with defined criteria that is indicative of successful project progress on a "critical path" activity, that if not achieved in a timely manner will inhibit the accomplishment of the expected project outcome in the allowable project period.

"Partner" means an organization that, in exchange for the right to the opportunity for a future financial return, has (1) agreed to provide matching funds for the proposed project or (2) entered into an agreement with the applicant organization relating to the commercialization of the proposed product.

"Subcontractor" means an organization (other than the applicant organization) that is expected to: (a) contribute to the scientific development or execution of the project in a substantive, measurable way *and* (b) receive $25,000 or more through the proposed project. "Subcontractor" does not include suppliers of widely available goods.

"Suspension Event" means a pre-defined condition that triggers a hold of CIRM funding until the suspension event has been resolved, if resolvable.