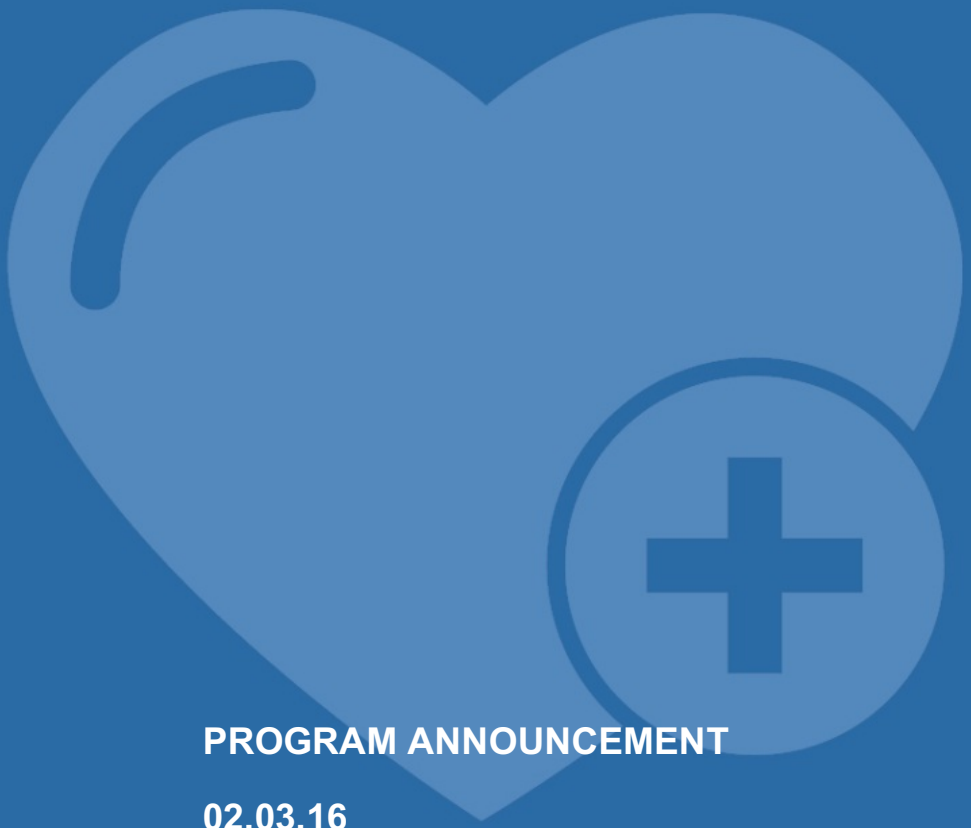
CLINICAL

Partnering Opportunity for Clinical Trial Stage Projects

CLIN 2



PROGRAM ANNOUNCEMENT

02.03.16

CLINICAL

Partnering Opportunity for Clinical Trial Stage Projects

(CLIN2)

Objective

The mission of California Institute for Regenerative Medicine (CIRM) is to accelerate stem cell treatments to patients with unmet medical needs.

The objective of this program announcement is to create a highly competitive partnering opportunity for promising stem cell-based projects to accelerate the completion of a clinical trial for a stem cell treatment that addresses an unmet medical need.

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.

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Award Information

What activities will CIRM support?

CIRM resources will support the following activities under this opportunity:

- ✓ Activities necessary for the conduct and completion of a Phase 1, Phase 2, Phase 3, Feasibility or Pivotal clinical trial under a single IND or IDE
- ✓ Manufacturing of product or the device to supply or conduct the proposed clinical trial
- ✓ Exploratory biomarker testing of samples from the clinical trial
- ✓ Assay development (e.g. potency assay)
- ✓ Stability testing
- ✓ Regulatory activities required for approval of the drug or device

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

- ✘ Early research and translation for candidate discovery/selection
- ✘ Formal comparability studies
- ✘ Manufacturing or process development activities to support clinical trials other than the trial proposed in the application
- ✘ Studies to remove a clinical hold by the FDA
- ✘ Construction or renovation of physical infrastructure

How will funds be awarded?

CIRM will disburse funds pursuant to a Notice of Award. Under the Grants Administration Policy for Clinical Stage Projects, awardees may elect to treat their award as a loan within ten years of the date of the award. (See GAP, sec. IV.) If an awardee does not make this election, the award will be treated as a grant. Except for the first payment issued upon initiation of an award, payments will be disbursed upon completion of specific Operational Milestones. **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 "Contingency Plan" under application components).

Eligibility

What types of projects are eligible for partnering?

To be eligible, the proposed project must satisfy the following requirements:

(1) 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.**

(2) Must propose a single clinical trial using a stem cell treatment or a device for use with a stem cell treatment

CIRM will support the completion of a single Phase 1, Phase 2, Phase 3, Feasibility, or Pivotal trial per award. If under an IND, the trial must test the safety and/or efficacy of a therapeutic candidate that is either:

- A cell therapy where stem or progenitor cells either compose the treatment or are used to manufacture the treatment. (Minimally manipulated bone marrow, minimally manipulated cord blood, or unmodified hematopoietic stem cells (HSCs) are eligible **only if** being developed as a novel method of addressing a rare or unmet need unlikely to receive funding from other sources.*****)
- A small molecule or biologic that (**i**) stimulates/recruits endogenous stem cells as the primary mechanism of action (MOA) for repair/regeneration OR specifically targets cancer stem cells as the primary MOA, and (**ii**) is being developed for a rare or unmet need unlikely to receive funding from other sources.*****

If under an IDE, the trial must test the safety and/or efficacy of a device that is:

- A device where human stem or progenitor cells either compose the device or are used to manufacture the device.
- A device intended for clinical use with a human stem or progenitor cell-based treatment.
- A device intended to address a critical bottleneck to clinical development or use of a stem cell treatment AND where testing with a human stem or progenitor cell confirms the clinical safety and efficacy of the device.

(3) Must have regulatory approval to proceed with proposed trial

- ***All applicants*** must have an active IND or IDE for the proposed candidate in the proposed indication before applying (i.e. the IND/IDE has been filed with FDA for >30 days and is not on clinical hold).

- ***Phase 2 trial applicants*** must have Phase 1 safety data supporting progression to Phase 2, obtained under the IND or IDE in an appropriate indication.*
- ***Phase 3 trial applicants*** must have compelling Phase 2 data for the same indication*, completed an End-of-Phase 2 meeting, and obtained FDA agreement on the trial design for Phase 3.
- ***Feasibility or Pivotal trial applicants*** must have obtained FDA agreement on the trial design under the IDE.

(4) Must include a project manager

The project team must include a project manager with experience in managing clinical development programs and able to devote at least 75 percent effort to the project.

(5) Co-funding requirements

CIRM will require applicants to co-fund at least the percentage of the total "Allowable Project Costs" indicated in the table below. Allowable Project Costs are those costs that: (1) are permitted under CIRM policies and regulations and (2) are for allowable project activities (see below). Allowable Project Costs include both 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. Funds requested from CIRM shall not exceed $20M. The co-funding may come from any funding source arranged by the applicant, but may not include "in-kind" or similar types of support. Applicants must commit at least the percentage of total Allowable Project Costs indicated below. Documentation demonstrating the commitment of funds to cover the proposed co-funding amount must be provided at the time of application submission (e.g., copy of executed term sheet showing amount of co-funding). Only funds that will be spent concurrently with CIRM funds (i.e., no sooner than ICOC approval and no later than completion of the final Operational Milestone) will qualify toward this co-funding requirement.

Minimum Percentage of the Total Allowable Project Costs the Applicant Must Provide

Applicant Type	Phase 1/Feasibility	Phase 2	Phase 3/Pivotal
Non-profit	None	40%	50%
For-profit	30%	40%	50%

(6) Must adhere to requirements for clinical trial sites in California

Applicant organizations located outside of California must have at least one clinical site in California.

California applicant organizations are expected to have clinical trial sites in California and must provide justification for inclusion of any sites located outside the State.

(7) For-profit organizations must demonstrate solvency

For-profit organizations must provide documentation that shows 180 days cash on hand from date of application submission and the financial ability to meet the co-funding and contingency requirements for the term of the project. The determination of solvency will be made at CIRM's sole discretion.

(8) CIRM applicant must be the IND sponsor

The IND/IDE sponsor (i.e., the entity named as the sponsor on the IND or IDE) for the proposed therapeutic or device must be the CIRM applicant organization if an organization-sponsored IND/IDE or the CIRM PI if an investigator-sponsored IND/IDE.

(9) Application must be accurate and complete

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

Who can apply and on what activities can funds be spent?

California Organizations

An organization (for-profit or non-profit) that employs and pays more than 50% of its employees in California is considered a "California Organization." A California Organization may use CIRM funds for the following allowable project activities:

- Activities conducted in California wholly in California; and
- Activities conducted outside of California, provided that: (a) the California Organization exercises direction, supervision and control over the activities and (b) the out-of-state organization that performs the activities does not retain intellectual property or publication rights in any intellectual property (e.g., invention, technology, data) arising out of the CIRM funded project.

Non-California Organizations

An organization (for-profit or non-profit) that has 50% or less of its employees in California is considered a "Non-California Organization." A Non-California Organization may only use CIRM funds for the following allowable project activities:

- Research activities conducted wholly in California, e.g., manufacturing, assay development, animal studies, biomarker testing, etc.;
- For preclinical research, activities that are directly required to support California activities. Allowable Project Costs under this paragraph include the share of preclinical costs that are directly required to support the California activities but exclude any costs recovered under paragraph (1) and the costs for project activities where an out-of-state organization performing the activities retains intellectual property or publication rights in any intellectual property (e.g., invention, technology, data) arising out of the CIRM funded project; and
- For clinical research, activities that are directly attributable to the treatment of California subjects. Allowable Project Costs under this paragraph include per subject share of costs but exclude any costs recovered under paragraph (1) and the costs for project activities where an out-of-state organization

performing the activities retains intellectual property or publication rights in any intellectual property (e.g., invention, technology, data) arising out of the CIRM funded project.

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

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 commit at least 30 percent effort to working on the project (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 partnering opportunity.

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Schedule and Deadlines

Applications Due	2:00 pm (PDT/PST) on the last business day of each month
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 130 days post submission)

Application Review Information

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 are encouraged to contact CIRM before applying with questions or to discuss their project's eligibility or scientific considerations. This is strongly advised for those applicants proposing a small molecule or biologic as the therapeutic candidate.

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, allow an opportunity to remedy, and if not timely remedied, terminate all further action on the application. In the event CIRM determines that the application does not meet the eligibility requirements of the program based on a subjective criterion (designated in the ELIGIBILITY section with an asterisk "*"), the applicant may request that the CIRM Grants Working Group (GWG) review the decision. This request must be submitted to CIRM no later than 14 days after the date of CIRM's notification that the application is ineligible. If the working group affirms CIRM's decision, the applicant will be notified and no further action will be taken on the application. If the GWG determines the application meets the eligibility requirements, the application will be accepted into the next available review cycle.

Budget Review

A team of budget professionals will review the proposed budget to provide information to CIRM regarding how the proposed costs compare with established market rates for similar activities (or how well the costs are justified when market rates are not established) and to confirm that costs designated as Allowable Project Costs comply with CIRM policies. When a proposed budget differs significantly from

market rates, adjustments to the budget will be required by CIRM prior to further review of the application. 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 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 http://www.cirm.ca.gov/GoverningBoard.

The fifteen participating scientists 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 the proposal's exceptional merit; 2) do not fund the project but allow for resubmission; or 3) do not fund the project and do not allow resubmission. 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's Application Review Subcommittee will make final funding decisions giving consideration to the GWG recommendations and any CIRM team recommendations.

Consideration of Past 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).

How will the scientific merit of an application be evaluated?

Scientific members of the GWG will evaluate and score applications based on the following key questions:

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

Does the proposed treatment fulfill an unmet medical need? Is the approach likely to provide an improvement over the standard of care for the intended patient population? Does the proposed treatment offer a sufficient, impactful, and practical value proposition for patients and/or health care providers?

2. Is the rationale sound?

Is the proposed project based on a sound scientific and/or clinical rationale? Is it supported by the body of available data? Do the data support the continued development of the treatment at this stage?

3. Is the project well planned and designed?

Is the project appropriately planned and designed to meet the objective of the program announcement and achieve meaningful outcomes to support further development of the therapeutic candidate? Is this a well-constructed, quality program? Do the project plan and 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? Does the team have a viable contingency plan to manage risks and delay?

Application Components and Submission

How does one apply?

Applications must be 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. A PI may submit only a single application in a given review cycle and may not submit additional applications during the review period.

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

What components does an application include?

The Grants Management Portal provides instructions for completing all the necessary components and submitting a final application. The application is designed to collect information necessary to appropriately evaluate the proposal and for CIRM to rapidly initiate an award if approved for funding. Applicants are required to indicate key personnel involved in the project, describe how the proposal addresses the objective of the partnering opportunity, provide a detailed plan of proposed activities, complete a detailed activity-based budget, and provide reference materials, such as FDA correspondence that confirms the status of the project. Applicants will also be required to provide a financial contingency plan that addresses how the applicant will cover possible funding shortfalls.

The main body of the proposal contains the following sections:

1. **Program Summary**
2. **Target Product Profile:** Outline of product specifications for the aspirational goals of the commercialized product
3. **Statement of Significance and Impact**
4. **Rationale:** Scientific rationale that supports use of the proposed treatment in the target disease or injury
5. **Preclinical Studies Summary:** Tabular summary of completed preclinical studies
6. **Previous Clinical Experience Summary:** Tabular summary of clinical data with the proposed or related product, if the proposed product has been previously tested or utilized in patients
7. **Risk/Benefit Profile**: Risk/benefit profile and draft of the Investigator's Brochure, if available
8. **Project Plan to Achieve the Program Announcement Objective**
9. **Timeline in Gantt Like Format**

10. **FDA Correspondence:** Relevant FDA comments and plan for addressing any issues raised by FDA and official FDA meeting minutes and/or FDA correspondence relevant to the proposed project

11. **Manufacturing Summary:** Manufacturing plan synopsis

12. **Clinical Protocol:** Clinical protocol synopsis and final clinical protocol

13. **Operational Plan:** Clinical operations plan for the proposed clinical trial

14. **Financial Contingency Plan:** Potential risks, mitigation strategies, and associated costs, including a description of a viable source to cover these costs (other than CIRM and not including co-funding)

15. **Team Organization:** Team structure, leadership and communications plan

16. **Resources and Environment:** Resources available to the project and environment

17. **References**

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. "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 Programs. Generally, project costs for personnel, supplies, travel, equipment, and subcontracts may be claimed. Limits for specific cost categories must be observed.

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What are Direct Facilities Costs?

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.

How much can an applicant claim for indirect costs?

For-profit organizations cannot claim indirect costs. For non-profit organizations, indirect costs will be limited to 20% of allowable direct research funding costs awarded by CIRM (i.e., 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.

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.

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.

Upon approval of an award, CIRM will appoint a Clinical Advisory Panel (CAP) to partner with the Awardee. The CAP 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. CAPs have the ability to enlist the help of CIRM's external subject matter experts when needed. Awardees will have ongoing communication with the CAP throughout the duration of the award, typically meeting by teleconference on a quarterly basis and in person once a year.

Other Requirements

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 http://www.cirm.ca.gov/reg/default.asp.

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Clinical Trials: Clinical trials funded by CIRM must be listed on http://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.

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Contacts

For information about this program announcement:

Send email correspondence to Clinical@cirm.ca.gov

or

Call our main line at 510-340-9101 and select “Funding Opportunities” then “Clinical”

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 conducts 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 that is indicative of project progress occurring as proposed in the application.

"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 project.

"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.