PRECLINICAL

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

PDEV: Funding Opportunity for Preclinical Stage Projects

Program Announcement

May 14, 2025

PDEV (Preclinical Development) Awards: Funding Opportunity for Preclinical Stage Projects

Summary

OVERVIEW			
Objective	To accelerate completion of preclinical development, FDA IND clearance, and clinical trial startup for stem cell-based and genetic therapies		
Scope	CIRM will support activities in the Pre-IND stage and/or the IND-enabling stage		
Program Recurrence	Twice per year		
AWARD DETAILS			
Maximum Award Amount	Up to $13,000,000 total cost		
Maximum Award Duration	Up to 5 years (60 months)		
Stage-specific Amount and Duration	**Stage**	**Early PDEV (Pre-IND)**	**Late PDEV (IND-Enabling)**
	Amount	$5,500,000	$7,500,000
	Duration	30 months (inclusive of maximum optional 6 months for candidate optimization)	30 months (inclusive of maximum optional 6 months for trial startup activity following IND clearance)
ELIGIBILITY REQUIREMENTS			
Applicant Organization	Only non-profit or for-profit organizations* that meet CIRM's definition of a California Organization* are eligible to apply		
Applicant PI	Must commit a minimum of 15% effort and adhere to CIRM's requirements*		
Critical Role	The project team must include an experienced project manager who commits a minimum of 50% effort		
Co-funding	**Unpartnered Non-Profit**: None Required **Non-Profit with For-Profit Partner**: 20% of allowable project costs **For-Profit**: 20% of allowable project costs The minimum co-funding requirement may be fulfilled by cash-based or warrant-based co-funding		
Stage Readiness	The application must provide data demonstrating that reproducible disease-modifying activity was achieved with the proposed candidate		
SCHEDULES AND DEADLINES			
Pre-submission Due	Twice per year		
Invitations to Apply	Approximately 30 days after pre-submission due date		
Application Due Date	Approximately 30 days after invitation to submit application		
GWG Review	Approximately 60 days after application submission due date		
Award Approval	Approximately 120 days after application submission due date		
Start Date	Must be ready to start award activities within 90 days of award approval		
CONTACT AND ADDITIONAL RESOURCES			
https://www.cirm.ca.gov/researchers/funding-opportunities-preclinical-research/ For additional information on the program or applications, contact preclinical@cirm.ca.gov. For questions related to the review and approval of applications, contact review@cirm.ca.gov. ***Additional requirements and definitions may be found in CIRM Funding Opportunities: Common Requirements and Definitions and are incorporated here by reference.**			

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Background

The mission of the 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. In September of 2024, CIRM's Governing Board, the Independent Citizens' Oversight Committee (ICOC), approved a Strategic Allocation Framework (SAF) to guide and optimize the value of CIRM's current and future investments. One key outcome of this exercise was defining an ambitious goal for CIRM, through its preclinical and clinical stage opportunities, to propel 15-20 therapies targeting diseases affecting Californians to late-stage trials.

The Preclinical Development (PDEV) program is a part of CIRM's core product development programs that unlike other funding sources, provide reliable and predictable funding throughout the award period, and bring expert CIRM staff and advice to support accelerated outcomes and advancement of projects along key stages of the product development pathway.

Through the PDEV Program, CIRM will support and accelerate preclinical development of transformative stem cell-based and genetic therapies. The PDEV program will advance a pipeline of innovative therapies for diseases affecting Californians to first-in-human clinical trials and will contribute toward the CIRM impact goal of advancing 15-20 therapies to late-stage clinical trials. Under this funding opportunity, CIRM will support preclinical development of stem cell-based and genetic therapeutic approaches that not only offer potential for transformative clinical impact but also meaningfully address current barriers to patient access and affordability.

Objective

The objective of this program is to accelerate the completion of preclinical development, FDA IND clearance, and clinical trial startup for stem cell-based and genetic therapies.

Under the PDEV 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.

This vision is achieved through critical path funding opportunities supporting research at different stages of maturity, with an emphasis on data and knowledge sharing, open innovation, and leveraging synergies across CIRM-funded programs, to propel therapeutic candidates to Phase I clinical trials.

Scope and Structure

CIRM will enable Awardees to complete all necessary preclinical development stage activities and achievement of IND clearance of a stem cell-based or genetic therapy candidate for eventual conduct of a first-in-human clinical trial. The expected outcome of all PDEV awards is the clearance of an IND application with the FDA for the stem cell-based or genetic therapy candidate.

Applicants may propose preclinical development activities ranging from candidate optimization to IND submission and trial startup. For purposes of the CIRM grant application and award contracting, the allowable project activities are divided into two stages: Early PDEV (pre-IND) and Late PDEV (IND-enabling).

Conduct of CIRM-funded pre-IND meeting, IND-enabling studies and GMP manufacturing activities in any given PDEV award will be subject to CIRM prior review with the exception of projects that have already conducted a pre-IND meeting for the proposed therapeutic candidate in the proposed disease indication prior to application submission.

Program funding areas

The PDEV Program aims to enrich the clinical pipeline with innovative stem cell-based and genetic therapies that have the potential for transformative clinical impact and which address barriers to patient access and affordability.

To support this goal, align with Proposition 14's mandate, and remain responsive to an evolving scientific and regulatory landscape, funding preferences will be set on an annual basis. These preferences will be guided by portfolio analyses and other strategic considerations in a cyclical manner. These preferences will be implemented through the PDEV pre-submission process (see "Pre-submissions", page 9) and via programmatic considerations by the Application Review Subcommittee of the ICOC.

Preference areas

For fiscal year 2025-2026 PDEV application cycles, the following modalities and project features will be prioritized:

PREFERENCE
Pluripotent stem cell-derived therapies
In vivo genetic therapies
Therapies using non-viral nucleic acid delivery
Projects addressing diseases of the brain and CNS
Projects progressing from DISC2 & TRAN1 Awards
Projects in which a pre-IND or INTERACT meeting has been conducted

Program activities

Applicants may request funds to cover costs for research activities conducted wholly in California and may also request costs for research activities conducted outside of California, provided that the California Organization exercises direction and control over the activities.

CIRM **will fund** the following activities under this opportunity:

	ALLOWABLE ACTIVITIES: EARLY PDEV (PRE-IND) STAGE
✓	All activities necessary to ready a human therapeutic candidate for pivotal IND-enabling preclinical studies including preparation and conduct of a pre-IND meeting with the FDA
✓	All activities necessary to optimize a candidate and to confirm disease-modifying activity for the finalized single human therapeutic candidate
	ALLOWABLE ACTIVITIES: LATE PDEV (IND-ENABLING) STAGE
✓	All IND-enabling activities necessary for submission and clearance of an IND with the FDA for a clinical trial with the therapeutic candidate
✓	Clinical trial startup activities to facilitate eventual rapid recruitment of patients
	ALLOWABLE ACTIVITIES: ACROSS ALL STAGES
✓	Activities associated with managing, preserving, and sharing data and knowledge from the project
✓	Activities associated with access and affordability planning for the therapeutic candidate in the proposed indication

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

	UNALLOWABLE ACTIVITIES ACROSS ALL STAGES
✗	The conduct of a clinical trial beyond start-up activities
✗	Patient recruitment, screening, or enrollment
✗	Activities already budgeted or paid for under a prior, existing or future CIRM award
✗	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
✗	Costs incurred on or before the date of ICOC approval

See Appendix A for examples of allowable activities under the PDEV award.

Award amount and duration

The expected outcome of all PDEV awards is the clearance of an IND application with the FDA for the stem cell-based or genetic therapy candidate. CIRM expects projects to advance in a timely manner through stages of preclinical development to IND clearance and will not accept applications under this program that propose project timelines in excess of limits described below.

Applicants may request CIRM support for preclinical development activities spanning pre-IND and IND-enabling stages. The maximum overall award amount and duration as well as expected funds requested and duration for each individual stage are described below.

MAXIMUM AWARD AMOUNT	MAXIMUM AWARD DURATION
$13,000,000	5 years (60 months)

STAGE	MAX STAGE AMOUNT	MAX STAGE DURATION
Early PDEV (Pre-IND)	$5,500,000	30 months (inclusive of maximum optional 6 months for candidate optimization)
Late PDEV (IND-enabling)	$7,500,000	30 months (inclusive of maximum optional 6 months for trial startup activity following IND clearance)

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

Funding allocation

CIRM anticipates funding between 12-21 PDEV awards in FY25-26, contingent on the ratio of Early PDEV and Late PDEV applications recommended for funding.

Provisional timetable

The PDEV funding opportunity will recur twice per year. The anticipated timeline of each funding cycle is as follows:

PROVISIONAL TIMETABLE	
Pre-submission Open	Twice per year, approximately spring and fall
Pre-submissions Due	Approximately 30 days after pre-submissions open
Invitation to submit application	Approximately 30 days after pre-submission due date
Applications Due	Approximately 30 days after invitation to submit application
Grants Working Group (GWG) Review	Approximately 60 days after application due date
Application Review Subcommittee (ARS) Award Approval	Approximately 60 days after GWG review
Award Start	90 days after award approval

Eligibility

All the following requirements must be fully satisfied for an application to be accepted and considered for funding by CIRM.

(1) The application must propose studies to support submission and clearance of a single IND application with the FDA for the proposed stem cell-based or genetic therapy.

Refer to CIRM Funding Opportunities: Common Requirements and Definitions for definitions of stem cell-based or genetic therapies in scope for the PDEV program. The overall project and proposed activities must fall within the defined scope of this opportunity.

(2) The application must demonstrate that the project is at the appropriate stage of readiness by providing data demonstrating that reproducible disease-modifying activity was achieved with the proposed candidate.

The application must provide data demonstrating that reproducible disease-modifying activity with the proposed stem-cell based or genetic therapy candidate was achieved under the following conditions. For this program, "candidate" refers to the drug product that would be carried forward in regulatory filings with FDA. While optimization is allowed as an activity in this program, a version of the candidate that could be advanced by the sponsor is required to meet the readiness requirement.

- Activity was demonstrated in preclinical model(s) relevant to the target clinical indication(s).
    - Recognizing that for certain genetic therapies no relevant preclinical model may exist, a proposal for such a genetic therapy shall provide an explanation regarding the lack of a relevant preclinical model and alternative data showing relevance to the target clinical indication.
- If the product is intended to be manufactured from a single cell source (e.g., an established cell line or monoclonal antibody), then the human therapeutic candidate proposed for clinical translation is identical to the test article that was used to demonstrate disease-modifying activity.
- If the product is intended to be manufactured from multiple cell sources (e.g., an autologous therapy or personalized allogeneic therapy), then disease-modifying activity must have been demonstrated with test articles that were generated using comparable manufacturing processes from at least two donor sources or cell lines.

Allogeneic Donor Cell Eligibility

For all projects developing a product candidate that includes allogeneic (donor-derived) cells:

- The cell source (tissue or cell line) proposed for use must have been consented by the donor for intended use and for clinical development and commercial sale.
- The cells must meet the Good Tissue Practices (GTP) requirements for donor eligibility (21 CFR 1271 (subpart C)), or there is plan in place to address the GTP requirements.

(3) The Principal Investigator (PI) must commit a minimum of 15% effort and adhere to CIRM's requirements.

The PI must commit a level of effort on the project consistent with achieving the PDEV program objective and not less than 15% on average over the project period. The PI must adhere to general eligibility requirements described in CIRM Funding Opportunities: Common Requirements and Definitions.

(4) The project team must include an experienced project manager at a minimum 50% effort

The project team must include a Project Manager with experience in managing relevant preclinical therapeutic development projects. The PM should be familiar with and utilize a variety of processes and tools to manage team communication, team dynamics, project budget, project schedule, project resources and project risks to help their team achieve the project objective in a timely manner. The Project Manager must commit at least 50% effort on average over the project period.

(5) The project team must include an experienced Data Project Manager

To ensure effective and collaborative sharing and management of data, a Data Project Manager must be part of the team. This individual must have demonstrated experience in data handling and is responsible for interfacing with a data management team(s), interfacing with CIRM's planned data infrastructure, reporting progress on data management and sharing as well as maintaining the integrity of data during ingestion. The

Data Project Manager role can be distributed among multiple people and may be fulfilled by Key Personnel with other critical roles.

(6) The applicant must be ready to initiate work on the funded project within 90 days of approval.

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded project within 90 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.**

(7) The application must be accurate and complete.

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

(8) The applicant organization must meet CIRM's definition of a California Organization.

The applicant organization must be a California organization per CIRM's definition described in CIRM Funding Opportunities: Common Requirements and Definitions at the time of application.

An institution or organization may submit more than one application per funding cycle under this opportunity.

(9) The applicant must propose 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. Co-funding requirements will be based on partnership status at the time of application. Applicants must also 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.

Allowable Project Costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy for Clinical Stage Projects 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 PDEV applicants must commit at least 20% 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 as part of the application and 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 legal@cirm.ca.gov for additional guidance and information on warrant-based co-funding.

Summary of Project Costs and Co-funding Requirements

APPLICANT TYPE	TOTAL CIRM-FUNDED PROJECT COST	MINIMUM CO-FUNDING REQUIRED
Non-profit	$13M	None
Non-profit with for profit Partner	$13M	20% of allowable project costs
For-profit	$13M	20% of allowable project costs

(10) For-profit organizations must demonstrate solvency.

Solvency requirements are defined in CIRM Funding Opportunities: Common Requirements and Definitions.

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

Applicants and their affiliates must represent and certify that they are in good standing, as described in CIRM Funding Opportunities: Common Requirements and Definitions.

Pre-submission and Application Preparation

Consultation and Webinars

CIRM staff aims to conduct public webinar(s) and Q&A sessions after posting of this program announcement. Prospective applicants are encouraged to sign up for email alerts and register for these sessions on our website. All pre-submission inquires will be addressed with written responses. CIRM may request that the applicant first complete a pre-submission intake form to facilitate informed responses to inquiries.

Prospective applicants who are invited to submit a full application will have the opportunity to request a consultation with CIRM Science Officers to address questions of eligibility, matching funds, budgets and other topics to improve alignment with program design and CIRM requirements.

Pre-submission Components and Evaluation

To ensure that the proposals most well-aligned with the scope, objectives and preferences of the program receive an in-depth scientific review by the GWG panel, CIRM will implement a pre-submission process for the PDEV awards. Pre-submissions are designed to gather required information to perform preliminary eligibility assessments, and to evaluate program fit.

All prospective PDEV applicants must submit an online pre-submission. The PDEV pre-submission must be completed through CIRM's online grant portal and includes the following sections:

- Online form
- Information on Core Team members, Project Title/Keywords and eligibility certifications
- Information on the project: project stage, therapeutic candidate, mechanism of action, indication, disease burden, value proposition, disease treatment landscape, major activities, prior regulatory interactions, prior CIRM funding
- Eligibility Upload Document: Data and information in support of candidate eligibility and readiness eligibility as described in CIRM Funding Opportunities: Common Requirements and Definitions and Eligibility criterion #2, respectively. All pre-submissions must use provided templates

Pre-submissions will be evaluated by CIRM staff to assess alignment with program objectives and scope, incorporating funding preferences set annually by the ICOC (see Scope and Structure, "Preference Areas").

Pre-submissions will be evaluated and ranked according to the following criteria:

- Proposition 14 Preferences:
    - Pluripotent stem cell-derived therapies
    - In vivo genetic therapies
    - Diseases of the brain and CNS

- Other Preferences:
    - Non-viral nucleic acid delivery
    - Progression from DISC2 and TRAN1 awards
    - Pre-IND or INTERACT meeting conducted
- Under-represented therapeutic/disease area: Targeting a therapeutic/disease area under-represented in CIRM active awards portfolio
- Novelty of therapeutic approach: Differentiation compared to CIRM active awards portfolio

Pre-submissions will NOT be evaluated for scientific merit or feasibility. Based on the above, a subset of pre-submissions will be selected for invitation to submit full applications. Selected pre-submissions will be evaluated for candidate and readiness eligibility requirements before being invited to submit a full application. No evaluation comments will be provided for pre-submission proposals.

How does one submit a Pre-submission or Application?

All pre-submissions and applications must be completed and submitted online using the CIRM Grants Management Portal at ***https://grants.cirm.ca.gov. A prospective PI must create a login in the system to access and submit pre-submission or application materials. Pre-submissions and applications are available in the system only to the PI. Invited full applications must be consistent with the pre-submission proposals. Applications deemed to be inconsistent will be disqualified at CIRM's discretion***.

What components does an Application include?

The PDEV application will be open to invited applicants only and 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.

In the online portal, invited applicants must fill out an eligibility form, indicate Key Personnel involved in the project, describe how the proposal addresses the objective of the funding opportunity, provide an overview of proposed activities, and prepare and justify an appropriate budget.

The application uploads page provides templates and guidelines for writing the Application Proposal, Biosketches, Project milestones and timelines, and other key components of the application. Applicants must use the provided templates. Applicants must describe all necessary activities to achieve the expected award outcome of IND clearance for the proposed therapy.

What are the contents of the Application Proposal?

The Application Proposal comprises the bulk of detailed information on the project, organized within the following sections. Page limits and formatting information will be provided on the actual Proposal template.

Resubmission Statement: If this application is a resubmission, then the applicant will provide a brief statement on how this application addresses the reviewers' critiques.

Project Summary: High-level summary of the project.

Target Product Profile: Template-based product label containing base case and optimal specifications for the proposed product.

Value Proposition: Description of the unmet medical need, affected patient population, demographic groups at risk, and existing treatment landscape for the target indication. Description of the proposed therapy's potential value to the affected patient population, caregivers, healthcare providers, and payors. Description of the potential for the proposed therapy to provide a substantial improvement in clinical outcomes for the affected patient population over available treatments and candidates in development. Description of the barriers to access and affordability of therapies for the affected patient population and whether the proposed therapy will meaningfully overcome such barriers.

Scientific Rationale: Explanation of how published and preliminary research findings support use of the proposed product as a therapy for the target indication. Description of how the study designs were informed by an understanding of the impact of genetic, environmental and other external factors on the affected patient population.

Preclinical Studies: Template-based tabular summary of completed pre-clinical studies that support achievement of the Program Announcement objective.

Clinical Studies: Template-based tabular summary of completed or ongoing clinical studies with the proposed or a related product.

Project Plan: Detailed description of all proposed activities that will support achievement of the Program Announcement objective organized by preclinical studies, chemistry manufacturing and controls (CMC) and clinical development as described below. Applicants requesting funding for both Early PDEV and Late PDEV stages will be required to describe plans for Late PDEV stage activities (i.e. IND-enabling activities) in sufficient detail to facilitate Grants Working Group review, and to clearly indicate what study designs will be pending FDA feedback. See Appendix A for examples of allowable activities under PDEV awards.

Preclinical Studies: Description of proposed preclinical studies to achieve Program Announcement objective. Template-based tabular summary of planned pre-clinical studies. Description of how relevant study designs are informed by an understanding of the impact of genetic, environmental and other external factors on the affected patient population.

CMC Development Plan: Brief description of the overall CMC development strategy for the proposed therapy including any completed manufacturing and analytical process development and GMP technology transfer activities. Description of all proposed CMC activities to achieve Program Announcement objective. Template-based description of proposed or current manufacturing and analytical process plan. Template-based draft quality target product profile and draft risk assessment (separate uploads).

Clinical Development Plan: Description of all proposed clinical planning activities to achieve Program Announcement objective. Description of how the clinical planning will be informed by an understanding of the impact of genetic, environmental and other external factors on the affected patient population. Description of completed and planned patient engagement strategies to inform clinical development planning activities. Template-based description of progress in the development of the protocol, clinical operations plans and trial enrollment goals for the first-in-human clinical trial for the proposed therapy.

Milestones: Tabular description of proposed project milestones and success criteria to achieve Program Announcement objective. Applicants will be required to provide a Gantt-format timeline of all proposed activities in a separate application upload.

FDA Correspondence: Template-based tabular summary of regulatory requests and proposed action plans.

Commercialization Plan: Detailed description of overall commercialization strategy for the proposed therapy in the target indication, including required stage-appropriate access and affordability planning activities and stage-appropriate commercialization and market access planning activities that will be conducted over the course of the award. Activities are described in CIRM Access & Affordability Planning Requirements.

Team Organization: Qualifications of the proposed team (including future stage-appropriate staffing needs) and plans for communication, decision-making and cross-functional team collaboration.

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

Resources & Project Environment: Description of dedicated facilities, equipment and resources that will support execution of the project.

Data Sharing Overview: A description of how raw data, processed data and metadata produced from the project will be made available to the research community consistent with FAIR (Findability, Accessibility, Interoperability, and Reusability) data sharing principles. Refer to CIRM Data Sharing and Management for additional information on how applicants should address data sharing and how the data sharing overview will be evaluated. Confirmation of participation in the PDEV Knowledge Network and description of potential knowledge sharing activities (described below).

References: Sources cited in the proposal.

What should one know about CIRM's requirements for Access & Affordability Strategic Planning?

Successful and rapid access to approved stem cell-based and genetic therapies requires stage-appropriate strategic planning throughout preclinical and clinical stages of development to ensure that the therapy is accessible and affordable for the affected patient populations. To help ensure that projects are adequately preparing for access and affordability, CIRM has developed a toolkit with a roadmap and associated

requirements for stage-appropriate strategic planning activities in preclinical and clinical development funding programs. Applicants must review the CIRM Access and Affordability Planning Requirements resource document for stage-appropriate PDEV activities, Applicants must adequately describe progress to date and propose a plan for conducting stage-appropriate activities in the PDEV application. Proposed access and affordability activities will be incorporated into PDEV award operational milestones. Applicants will be required to report progress on commercialization and market access activities.

What should one know about CIRM's data sharing and knowledge sharing requirements for the PDEV program?

CIRM requires PDEV awardees to manage and preserve raw data, processed data and metadata, and share applicable data (see Data Terminology in CIRM Data Sharing and Management). CIRM also requires applicants to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing data produced from the funded project. CIRM also intends to build a knowledge network of PDEV awardees to help all CIRM-funded projects accelerate therapies to first-in-human clinical trials (described below). At application submission, the applicant agrees to participate in the PDEV Knowledge Network.

CIRM recognizes the balance between protecting intellectual property prior to commercialization and CIRM's commitment to open science and innovation, and as such there may be aspects of applicable data generated as part of PDEV awards which could be treated as confidential until filing for patent protection, as trade secrets with requisite enhanced company protection, or in advance of regulatory approval. Data and knowledge sharing will be maximized to the extent that is possible. Refer to CIRM Data Sharing and Management for additional information on how PDEV applicants should address data sharing and how the data sharing overview will be evaluated.

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. The total CIRM Award is subject to a total Award cost cap of Allowable Project Costs. Allowable Project Costs are detailed in the CIRM Grants Administration Policy for Clinical Stage Projects and includes Direct Facilities and Indirect Costs. Generally, project costs for personnel, supplies, travel, equipment, and subcontracts may be claimed. Limits for specific cost categories must be observed.

Applicants requesting CIRM funding for both Early PDEV and Late PDEV stages of activities will be required to detail activities-based costs for both stages at the time of application submission.

For any proposed subcontracts over $500,000, a tabulated summary of at least three proposals must be provided and the selection of the subcontractor must be justified in detail. If any such subcontracts are sole sourced, detailed justification must be provided. The Resources section of this PA describes optional available resources for CIRM-funded projects including the CIRM academic GMP Manufacturing Network and the CIRM Industry Resource Partners composed of reagent, equipment and service providers (i.e. CDMOs, CROs, etc.).

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 costs for for-profit awardees or any non-profit awardees without a federally negotiated Facilities & Administrative Rate agreement are limited to 35% of direct project costs and must be consistent with facilities rates applied to similar research awards at the organization. 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 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.

Change in Status

Applicants are required to notify CIRM of any material change in status while the application is pending review (e.g., change in PI, the applicant no longer qualifies as a California Organization, etc.).

Application Review Information

What is the process for evaluating a full application?

Eligibility Review

CIRM will assess whether the proposed project meets eligibility requirements sought under this program and confirm that the application reflects what was outlined in the pre-submission. If CIRM determines, in its sole discretion, that an application does not meet the eligibility requirements of the program or that the submitted application is incomplete or contains false or inaccurate information, 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.

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 or nurse members of the ICOC (called "GWG Board Members"), and the Chair of the ICOC. The list of scientific members who may participate in the GWG review, as well as GWG bylaws and policies, can be found at https://www.cirm.ca.gov/about-cirm/working-groups/. The composition of the ICOC can be viewed on the CIRM website https://www.cirm.ca.gov/about-cirm/about-board/.

The fifteen participating scientists on the GWG will evaluate the applications and score them on a scale of 1-100 according to scientific and technical merit, applying the review criteria described below. For purposes of making funding recommendations to CIRM's board, each application shall be assigned to one of two categories based on the median score as follows:

Median score 85 or above: The application has exceptional merit and warrants funding, if funds are available; or

Median score below 85: The application is not recommended for funding.

The Application Review Subcommittee of the ICOC will make final funding decisions.

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?

Applications will be scored based on the following review criteria.

1. **Value Proposition -** *Evaluate the extent to which the therapy offers a compelling value proposition based on holistic consideration of the following.*
   - Assess the therapy's potential to provide a meaningful and substantial improvement in clinical outcomes for the intended population as compared to therapies currently available or in trials (e.g., efficacy, safety, patient burden).
   - Assess the expected impact of addressing the unmet medical need on patients, caregivers, and the healthcare system.
   - Assess the therapy's potential to be more accessible and affordable compared to available treatments or therapeutics currently in clinical development for the intended patient population and healthcare system.
   - Evaluate the feasibility and practicality of the therapy's uptake by patients, caregivers, and the healthcare system.
2. **Rationale -** *Evaluate the scientific rationale for the proposed therapy and the strength of the supporting data.*
   - Assess the fundamental robustness of the scientific rationale, including justification for the indication, therapeutic approach, and route of administration.
   - Assess the extent to which the rationale is supported by the body of available data. For example, consider whether there is compelling evidence of disease modifying activity in a relevant model.
   - Consider the strengths & limitations of the data presented and/or the models utilized in completed studies.
3. **Project Plan & Design -** *Evaluate the project's plan and design to achieve an active IND.*
   - Evaluate the extent to which the proposed activities are necessary and appropriate to efficiently and effectively progress the project to IND clearance. For example, consider proposed preclinical studies, IND-enabling studies, process and analytical development/testing, clinical protocol drafts and trial startup activities as stage-appropriate.
   - Consider whether the PDEV objective will be achieved within the proposed budget and timeline.
   - Assess the validity of the potential project risks identified along with the mitigation and contingency plans presented.
   - Assess how well the project incorporates stage-appropriate access and affordability planning to support future market access.
4. **Project Team and Resources -** *Evaluate the expertise and resources that will be deployed to achieve the project deliverables.*
   - Evaluate the appropriateness of the team's leadership, expertise, and staffing plan to successfully navigate to IND clearance. For example, consider team leadership, expertise and staffing in relevant functional areas such as non-clinical, GMP manufacturing, analytical, regulatory and clinical.
   - Consider whether a robust plan for coordination and execution of the project has been clearly outlined.
   - Assess the extent to which the team has access to all necessary resources and facilities, including manufacturing facilities, to successfully conduct the proposed activities.
   - Consider whether the collective team, including consultants and subcontractors, have a demonstrated track record of supporting stem cell-based and genetic therapy projects to clinical trials.
5. **Population Impact** - *Evaluate the extent to which the project considers the potential impact of the proposed therapy across affected populations.*
   - Evaluate the applicant's understanding and consideration of genetic, environmental and other external factors that may impact on the adoption, effectiveness or safety of the proposed therapy.
   - Assess the appropriateness of the intended clinical study population in the context of the project stage and current knowledge of demographic groups at risk for the target indication.

- Evaluate the extent to which the applicant's prior or proposed activities incorporate perspectives and experience from patients and individuals affected by the target indication.

Budget Review

CIRM will review the proposed budget to ensure all costs are reasonable, allocable, consistently treated and allowable. When CIRM determines that 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, CIRM will adjust the budget prior to issuance of an award based upon assessments of the GWG, the CIRM team, or by the Application Review Subcommittee of the ICOC.

Award Administration

Issuance of Award

CIRM issues awards through a Notice of Award (NOA), which serves as the official contract defining terms, conditions, and funding commitments. Before finalizing the NOA, CIRM reserves the right to modify project activities and budgets, including improving data sharing plans submitted during pre-funding administrative review. After consulting with project teams, CIRM establishes milestones, success criteria, and timelines based on application information and data sharing plans and may consult external advisors when developing operational milestones for research, data sharing, and access and affordability planning activities. CIRM will also review key agreements critical to project success to ensure compliance with applicable policies and regulations.

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 Award based upon information provided in the Application. CIRM may consult with external advisors to inform development of operational milestones for the proposed research and/or access and affordability planning activities. 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.

An award progressing from Early PDEV (Pre-IND) to Late PDEV (IND-enabling) milestones will be reviewed by CIRM. Milestones may be re-budgeted and amended in consultation with the project team as needed prior to start of IND-enabling activities. Any unused funds after completion of the Early PDEV (Pre-IND) stage may be rolled over to the Late PDEV (IND-enabling) stage of the award with appropriate justification from the project team and prior approval from CIRM.

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. If a Suspension Event is not resolved to CIRM's sole satisfaction, CIRM has the right to terminate the award. CIRM establishes Suspension Events for inclusion in the NOA based on information provided in the Application.

Product Development Expert Network

To facilitate effective management of PDEV awards and collaborative partnership with PDEV project teams, CIRM will utilize a network of contracted external subject matter experts in relevant domains such as: CMC, clinical, pre-clinical, and regulatory strategy. At its discretion, CIRM will leverage the PDEV Expert Network to provide guidance on individual PDEV projects to help achieve the program objective. For example, experts may be called upon to advise on milestone achievement, to provide guidance on regulatory interactions, and to provide guidance on addressing FDA feedback. CIRM may enlist additional expertise on an ad-hoc basis depending on the needs of an award. PDEV awardees planning to conduct a pre-IND meeting during a PDEV award will be required to review the pre-IND strategy and pre-IND package with CIRM and PDEV Expert Network advisors prior to submission to the FDA.

Reporting

Awardees will be required to provide periodic written progress and financial reports to CIRM. CIRM will partner with the awardee to foster the success of the project. Awardees will have ongoing communication with the CIRM Science Officer throughout the duration of the award, typically meeting by teleconference and periodically in person. Key personnel responsible for critical process development and manufacturing activities may be required to submit progress reports to CIRM.

Data Sharing and Management

The sharing of data and knowledge produced from CIRM-funded projects is key to advancing the field of regenerative medicine and accelerating the discovery, validation and development of treatments for patients. CIRM requires awardees to manage and preserve raw data, processed data, and metadata, and make applicable data and metadata available to the broader scientific community. CIRM also requires applicants to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing data produced from the funded project. Refer to CIRM Data Sharing and Management for additional information on how applicants should address data sharing and how the data sharing overview will be evaluated. The requirements described in CIRM Data Sharing and Management are incorporated here by reference.

Knowledge Network

CIRM intends to build a knowledge network of PDEV awardees to help all CIRM-funded projects accelerate therapies to first-in-human clinical trials. The PDEV Knowledge Network will facilitate pre-competitive sharing of knowledge and resources between CIRM awardees to help advance best practices for preclinical development in areas such as, but not limited to, regulatory interactions, pre-clinical study designs, assay development, clinical trial design, clinical trial operations planning, and access and affordability planning. PDEV Knowledge Network activities may consist of thematic workshops, direct knowledge exchange between awardees, collaboration between awardees on project activities, sharing of relevant resources, etc. CIRM recognizes the balance between protecting intellectual property prior to commercialization and CIRM's commitment to advancing best practices for preclinical development across its program portfolio and thus will encourage pre-competitive knowledge sharing between awardees to the best extent possible.

CIRM Regulations

Grant awards made through this PA will be subject to all applicable CIRM regulations. These regulations can be found at https://www.cirm.ca.gov/our-funding/cirm-stem-cell-grant-regulations.

Resources

CIRM-Funded Infrastructure

CIRM has established a set of Infrastructure Programs to help accelerate development of stem cell-based and genetic therapies.

The CIRM Alpha Clinics are a statewide network composed of nine leading California Medical Centers. The Network supports stem cell-based and genetic therapy clinical trials for academic and commercial partners. Applicants and awardees can choose to partner with the CIRM Alpha Stem Cell Clinics Network to identify California trial sites, evaluate patient cohorts, and accelerate trial initiation and completion.

The CIRM Cell and Gene Therapy Manufacturing Network is composed of nine non-profit GMP manufacturing facilities that are co-located with the Alpha Clinics. Applicants and awardees can choose to utilize the Network GMP facilities for process development, manufacturing, quality control testing and other related services.

CIRM Industry Resource Partner Program

The CIRM Industry Resource Partner Program is composed of select contract development and manufacturing organizations (CDMOs), contract research organizations (CROs) and other vendors and service providers that are committed to making their consultations, services, and resources more accessible to CIRM-funded projects.

CIRM does not require that applicants and awardees utilize Alpha Clinics, Manufacturing Network, or Industry Resource Partners; applicants and awardees are expected to conduct their own evaluation of the suitability of these resources for their proposed project.

Applicant Resources

- For scientific questions that are not addressed in the above resources, send email correspondence to preclinical@cirm.ca.gov.
- For questions related to application review, send email correspondence to review@cirm.ca.gov.
- For questions related to budgets or allowable project costs, please consult the Grants Management FAQ on CIRM's website under "For Researchers > Grants > Managing your Grant"
- Terms used here are defined in CIRM Common Requirements and Definitions.
- Information about CIRM's data sharing requirements, data sharing and management guidelines, and applicant resources are found in CIRM Data Sharing and Management.
- Requirements and guidelines to address access and affordability planning are available in Access and Affordability Planning Requirements

Appendix A

Examples of allowable activities by category and stage of development include, but are not limited to, the following:

CATEGORY	EARLY PDEV (PRE-IND) STAGE	LATE PDEV (IND-ENABLING) STAGE
Nonclinical	• Conduct of non-clinical pilot studies including pharmacodynamic, pharmacokinetic (cell biodistribution/fate), immunogenicity, pilot safety and mechanism of action (MOA) studies • Studies to select indication, dose, treatment regimen and route of administration • Optimization of delivery mechanisms for therapeutic candidate • (Optional) Optimization of candidate(s) including cell/tissue source, gene engineering/editing components, delivery mechanism, etc. • (Optional) In vitro and in vivo studies for lead optimization, optimization of route of administration / delivery method, and / or demonstration of disease-modifying activity with optimized candidate	• Conduct of IND-enabling non-clinical GLP studies including pharmacodynamic and pharmacokinetic studies, safety and toxicology studies, MOA and efficacy confirmation.
CMC	• Preparation of cGMP-compliant master and working cell banks • GMP-compatible process scale-up/development sufficient to supply phase 1 trial and transfer to GMP manufacturing • Analytical assay development and qualification (i.e. in-process and release assays, stability, activity, potency) • Manufacturing of therapeutic candidate(s) to support project activities • Development of Quality Target Product Profile (QTPP), critical quality attributes/critical process parameters (CQA/CPP) and performance of manufacturing risk assessment	• GMP manufacturing of the therapeutic candidate to support IND-enabling studies or to supply the intended clinical trial • Process development and transfer to GMP manufacturing • Analytical assay development and qualification (i.e. in-process and release assays, stability, activity, potency) • Development of Quality Target Product Profile (QTPP), critical quality attributes/critical process parameters (CQA/CPP) and performance of manufacturing risk assessment
Clinical Planning	• Development of a comprehensive clinical plan that incorporates patient perspectives • Development of clinical protocol synopsis and draft clinical protocol for a phase 1 trial • Patient advocate and community engagement to inform clinical planning	• Clinical protocol development, informed by patient perspectives, for the planned first-in-human trial • Development of clinical operations plan including patient outreach, engagement, recruitment and retention strategies to meet trial participation goals • Patient advocate and community engagement to inform clinical planning

Regulatory	• Preparation for and conduct of an INTERACT meeting with the FDA • Preparation for and conduct of a Pre-IND meeting with the FDA	• Preparation and submission of the IND package to the FDA
Access & Affordability Strategic Planning	• Reimbursement and market access strategy planning • Market landscape research	• Reimbursement and market access strategy planning • Market landscape research