CLINICAL

CIRM
CALIFORNIA'S STEM CELL AGENCY

CLIN2: Funding Opportunity for Clinical Trial Stage Projects

PROGRAM ANNOUNCEMENT
08.08.22

CLIN2: Funding Opportunity for Clinical Trial Stage 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 completion of a clinical trial for a regenerative medicine-based therapy (stem cell-based or genetic therapy) 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.

Contact

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.”

CIRM

CALIFORNIA'S STEM CELL AGENCY

Award Information

What activities will CIRM fund?

CIRM funds **will** support the following activities under this opportunity:

- ✓ All activities necessary for the conduct and completion of a clinical trial with a single therapeutic candidate or medical device
- ✓ Correlative studies associated with the current proposed trial such as elucidating mechanism of action, biomarker identification, patient selection
- ✓ Manufacturing of product to supply the proposed clinical trial, including a follow on clinical trial, where appropriately justified
- ✓ Commercial development activities including pharmacoeconomic analysis
- ✓ Product development activities to support the clinical trial or clinical development
- ✓ Comparability studies
- ✓ Activities intended to promote and uphold principles of Diversity, Equity, and Inclusion (DEI) in the conduct of the study
- ✓ Activities associated with sharing data and knowledge from the study

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

- ✗ 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

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 CLIN2 project are limited to:

- For first in-human clinical trial studies with the therapeutic candidate (or feasibility studies if the product is a medical device) in a specific disease indication and using a given route of administration
  - $12,000,000 per award to a non-profit awardee; and
  - $8,000,000 per award to a for-profit awardee
- For succeeding clinical trial studies conducted after a first in-human trial with the therapeutic candidate in a specific disease indication and using a given route of administration
  - $15,000,000 per award for either a non-profit or for-profit awardee
- 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. The proposal must aim to enroll and dose all patients in the trial and to complete initial analysis of the trial's primary endpoint(s) within the maximum 48 month timespan. Patient follow-up activities within the 48 month award period are allowed. Further follow up beyond 48 months consistent with FDA regulations is expected but not allowed under this funding mechanism.

CIRM

CALIFORNIA'S STEM CELL AGENCY

Eligibility

What types of projects are eligible for funding?

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

(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 regenerative medicine-based therapy (stem cell-based or genetic therapy)

CIRM will support the completion (as defined in the Award Information section on page 3) of a single clinical trial (phase 1, 2, or 3) per award to test the safety and/or efficacy of a therapeutic candidate as follows:

- ✓ A cell therapy where human stem or progenitor cells[1] (collectively, "stem cells") either compose the therapy or are used to manufacture the cell therapy. 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.

- ✓ A genetic therapy[2] approach (i) that targets a human somatic cell for its therapeutic effect **AND** (ii) is intended to replace, regenerate, or repair the function of aged, diseased, damaged, or defective cells, tissues, and/or organs.

- ✓ A small molecule or biologic that acts on or is dependent on endogenous human stem cells for its therapeutic effect, that is dependent on targeting human cancer stem cells for its therapeutic effect, that modifies a stem cell therapy, **OR** where a human stem cell is necessary to manufacture the therapy (e.g., extracellular vesicles).

---

1 Under Proposition 14, progenitor cells are "multipotent or precursor cells that are partially differentiated but retain the ability to divide and give rise to differentiated cells."
2 For the scope of this solicitation, CIRM considers genetic therapy to mean a human therapeutic intervention that: 1) alters the genomic sequence of cells or 2) introduces or directly manipulates nucleic acids (such as mRNAs, antisense oligonucleotides) in cells. The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, or introduce new or modified nucleic acids that augment the therapeutic potential of the target cells.

CIRM

CALIFORNIA'S STEM CELL AGENCY

Device trials

Under an IDE CIRM will support a phase 1 or feasibility trial of a medical device (including a diagnostic device) as follows:

- ✓ A medical device where human stem cells are a necessary component of the device or are used to manufacture the device.
- ✓ A device intended for clinical use with a genetic therapy or human stem cells where the genetic therapy or stem cell contributes to the therapeutic mechanism of action (MOA) of the combination product.
- ✓ A device intended to address a critical bottleneck to clinical development or use of a genetic therapy or stem cell treatment AND where testing with a genetic therapy or human stem or progenitor cell confirms the clinical safety and efficacy of the device.
- ✓ A device where the therapeutic MOA requires the recruitment or incorporation of an endogenous stem cell.

(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 has approval to proceed with the proposed clinical protocol). The applicant must provide communication from FDA indicating it is safe to proceed with the proposed clinical protocol if proposing a new trial under an open IND/IDE.

Phase 2 trial applicants must have Phase 1 safety data obtained with the proposed treatment in an appropriate indication unless agreement to proceed with the Phase 2 protocol is otherwise indicated by the FDA.

Phase 3 trial applicants must have Phase 2 data for the proposed indication(s) and have completed the End-of-Phase 2 meeting or equivalent.

(4) Must include a project manager

The project team must include a project manager with experience managing clinical development programs and able to devote at least 50 percent effort to the project.

(5) Must demonstrate appropriate level of co-funding

CIRM will require co-funding from the applicant based on the total "Allowable Project Costs" as indicated below. 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. 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 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 by the application deadline (e.g., copy of executed term sheet showing amount of co-funding, conditions, and source) and by the project start date the awardee must have

cash-on-hand to co-fund the first operational milestone disbursement. 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

- For first in-human clinical trial studies with the therapeutic candidate (or feasibility studies if the product is a medical device) in a specific disease indication and using a given route of administration
    - 30% for for-profit awardee
    - None for non-profit awardee
- For succeeding clinical trial studies conducted after a first in-human trial with the therapeutic candidate in a specific disease indication and using a given route of administration
    - 40% for for-profit and non-profit awardees

(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/IDE 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.*

(10) 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.

(11) CIRM/NHLBI Cure Sickle Cell Disease Joint Initiative (currently not accepting applications for this initiative)

All applications proposing a therapeutic candidate or medical device for the treatment of sickle cell disease will be considered for funding under the CIRM/NHLBI Cure Sickle Cell Disease Joint Initiative and all application materials will be shared with appropriate NHLBI staff. Under this program, successful applicants are awarded funds from both CIRM and NHLBI. Co-funded projects must adhere to the NHLBI Data and Safety Monitoring and NHLBI Data Sharing policies and are required to share aggregate clinical trial data with the Cure Sickle Cell initiative's designated Data Coordinating Center.

Who 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:

- ✓ The per subject share of the costs of clinical and non-clinical research activities that are directly attributable to the treatment of subjects enrolled in the proposed clinical trial; and
- ✓ Costs of manufacturing activities for a subsequent clinical trial when applicant adequately justifies conducting such activities during the proposed clinical trial

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:

- ✓ The per subject share of the costs of clinical and non-clinical research activities, whether conducted in California or outside of California, that are directly attributable to the treatment of California subjects enrolled in the proposed clinical trial; and
- ✓ Costs of manufacturing conducted in California for the proposed clinical trial for subjects enrolled, provided such costs are deducted before calculating the per subject share of costs; and

CIRM

CALIFORNIA'S STEM CELL AGENCY

- ✓ Costs of manufacturing conducted in California for a subsequent clinical trial when the applicant adequately justifies conducting such activities during the proposed clinical trial

Unallowable Costs

For both California Organizations and Non-California Organizations, Allowable Project Costs do NOT 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. Unallowable costs also include project costs incurred before the date the ICOC approves the application for funding, which can be as early as 90 days post application 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 partnering opportunity.

CIRM

CALIFORNIA'S STEM CELL AGENCY

- Must **not** currently have another application that is substantially similar or has overlapping activities pending review or approval under any CIRM opportunity.

CIRM

CALIFORNIA'S STEM CELL AGENCY

Application Review Information

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 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 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 the proposed costs compare with established market rates for similar activities, 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, 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. 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.

CIRM

CALIFORNIA'S STEM CELL AGENCY

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 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 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 6 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).

How will the scientific merit of an application be evaluated?

Scientific members of the GWG will evaluate and score applications based on the following 5 review criteria:

CIRM

CALIFORNIA'S STEM CELL AGENCY

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

Does the proposed treatment address 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 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?

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

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? Manufacturing plays an important role in clinical projects. Accordingly, is the proposed manufacturing plan appropriately designed and budgeted for both time and cost? Do the project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission (i.e. Are the proposed experiments essential and do they create value that advances CIRM's mission? Is the timeline appropriate to complete the essential work without unnecessarily extending it for non-essential activities)?

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, appropriate facilities and expertise to conduct the proposed activities, including manufacturing? Does the team have a viable contingency plan to manage risks and delay?

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

Does the applicant understand the race, ethnicity, sex, gender, and age-based health disparities associated with the target indication? Has the applicant presented an appropriate rationale for the proposed trial study population that is based on current knowledge of the demographic groups at risk for the target indication, including underserved populations? Has the applicant developed goals to achieve an inclusive distribution of subjects by race, ethnicity, sex, gender, and age? Has the applicant provided adequate justification for the proposed exclusion of any group(s) at risk for the target indication?

Does the plan for trial outreach, engagement, enrollment, and retention address key barriers to trial participation faced by underserved demographic groups? Is the plan well-matched to the needs of the proposed trial population, and feasible in the proposed time frame? If activities for building cultural sensitivity on the team are proposed, are they well-matched to the needs of the project and feasible in the proposed time frame?

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. 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 Data Sharing and Management Plan (DSMP), a detailed Activity-Based Budget, and an application uploads section for reference documentation including Key Personnel Biosketches, IND sections, FDA correspondence and Manufacturing Plan.

What are the contents of the Proposal?

Project Summary: High-level summary of the project.

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

Value Proposition: Description of the unmet need and the product's potential value to patients, healthcare providers and caregivers.

Diversity, Equity, and Inclusion (DEI): Statement describing how the project will help fulfill the unmet medical needs of the diverse California patient population. See full description below.

Scientific Rationale: Explanation of how published and preliminary research support use of the proposed product as a therapy or medical device for the target indication.

IND- or IDE-Enabling Studies: Template-based tabular summary of IND- or IDE-enabling study results.

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

Gantt-Like Timeline: Timeline for all proposed activities.

Project Plan: Description of all proposed activities detailing how the objective of the Program Announcement will be met.

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

Manufacturing Plan Synopsis: Template-based synopsis describing key aspects of the manufacturing plan for the proposed trial.

Trial Protocol Synopsis: Template-based synopsis describing key aspects of the protocol for the proposed trial.

Clinical Operational Plan Synopsis: Template-based synopsis describing key aspects of the planned clinical operations for the proposed trial.

Plans for Risk Mitigation & Financial Contingency: Potential risks, 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 and inclusive commercial development of the product.

References

How does one address Diversity, Equity, and Inclusion (DEI)?

In the DEI section of the proposal, all applicants for the CLIN2 program must characterize race, ethnicity, sex, gender, and age-based health disparities associated with the target indication and set goals for a trial study population that are based on current knowledge of the demographic groups at risk for the target indication, including underserved populations. Applicants should also aim to achieve an inclusive distribution of subjects by race, ethnicity, sex, gender, and age. Applicants must provide adequate justification for the proposed exclusion of any group(s) at risk for the target indication.

CLIN2 applicants must then provide a clear and robust plan for trial outreach, engagement, enrollment, and retention activities intended to address key barriers to trial participation faced by underserved demographic groups. Plans may include, for example, alliances with community clinics, designating community liaisons, social network outreach, distribution of printed materials, patient navigators, transportation and lodging, call centers, translation services, or child and/or pet care.

Finally, applicants for the CLIN2 program can propose activities for building cultural sensitivity on the team and/or at partner institutions. Activities may include, for

example, implementing published guidance for cultural sensitivity in clinical care, training for team members in culturally responsive clinical skills, or convening a panel for guidance and oversight.

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.

What is required for the Data Sharing and Management Plan?

The sharing of data and knowledge produced from CIRM-funded projects is key to advancing the field of regenerative medicine and accelerating treatments to patients. CIRM requires its awardees to develop and execute a Data Sharing Plan that includes management and preservation of data and making applicable data available to the broader scientific community. CIRM also requires sharing of data in accordance with FAIR data principles through established repositories including, but not limited to, specialized NIH-supported repositories, generalist repositories, cloud platforms and institutional repositories. The Data Sharing Plan must be included in the application and the plan is subject to evaluation by the Grants Working Group. Applicants are required to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing data produced from the funded project. The repository selected and summary of the data shared must be reported to CIRM during and after the project period. To promote the generation of knowledge CIRM may publicly share where CIRM-funded data are deposited.

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

CIRM

CALIFORNIA'S STEM CELL AGENCY

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.

How much can an applicant claim for indirect costs?

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 6 leading California Medical Centers (https://www.cirm.ca.gov/patients/alpha-clinics-network). The Network has performed over 40 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 patient cohorts and accelerate trial initiation and completion.

CIRM

CALIFORNIA'S STEM CELL AGENCY

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 to provide clinical trial enrollee demographic data in the trial population categories as specified in the application 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 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.

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.

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

CIRM

CALIFORNIA'S STEM CELL AGENCY

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 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.

CIRM

CALIFORNIA'S STEM CELL AGENCY

Recent Document Revisions

Date	List of Changes
08/08/2022	• Revised candidate eligibility to be the same for all clinical trial phases • Clarified trial enrollment demographic data requirement
06/08/2022	• Updated CIRM's Mission • Updated the Objective of the Program Announcement • Changed basis for determining maximum award amounts • Changed basis for determining applicant co-funding amount • Replaced the requirement for (i) a statement on addressing the underserved and (ii) a statement on promoting and upholding principles of Diversity, Equity and Inclusion (DEI) with a unified application section on DEI; updated review criterion 5 accordingly • Updated review criteria to include manufacturing questions • Updated application components to include the Data Sharing and Management Plan • Updated names and descriptions of Proposal sections

07/01/2021	• Revised candidate eligibility:
	  ○ Removed requirement for gene therapy, small molecule, and biologic candidates to be developed for a rare or unmet need unlikely to receive funding from other sources
	  ○ Gene therapy-related device trials are eligible
	• Added additional clarification language to requirement for diversity, equity and inclusion in research

01/01/21	• Adjusted maximum award amount and duration
	• Revised project start time
	• Revised percent effort requirement for project manager:
	  ○ Project manager must devote at least 50% effort to the project.
	• Clarified therapeutic candidate eligibility:
	  ○ Gene therapy projects do not require a "vital research opportunity" vote by GWG under Prop 14.
	  ○ Clarified that minimally manipulated bone marrow and HSC are eligible for phase 2 and 3 proposals.
	• Added Data Sharing Plan Requirement.
	• Added review criterion for serving the needs of underserved communities.
	• Added requirement to address diversity, equity and inclusion in research.
	• Updated Prop 14 definitions.
	• Added paragraph regarding CIRM/NHLBI Sickle Cell Initiative requirements.

CIRM

CALIFORNIA'S
STEM CELL
AGENCY