CALIFORNIA'S STEM CELL AGENCY

Funding Opportunity Concept Plan

CLIN2: CLINICAL TRIAL STAGE PROJECTS

BACKGROUND

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

Through the CLIN2 program, CIRM continues to create funding opportunities for the types and stages of clinical research that otherwise do not exist or are of limited scope and focus to advance the field of regenerative medicine. Existing federal funding opportunities for clinical trial stage activities are primarily driven by the internal priorities and interests of the administering body and, therefore, are unpredictable and limited in both scope and focus. The CLIN2 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 towards obtaining marketing approval. CIRM therefore provides this unique opportunity to California scientists to support stages in the development of clinical research projects that are unlikely to receive timely or sufficient funding from other sources.

OBJECTIVE

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 and to advance development of such therapies to marketing approval.

AWARD INFORMATION

What activities will CIRM fund?

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

- All activities necessary for the conduct and completion of a first-in-human ~~phase 1,~~ or follow-on ~~phase 2, or phase 3~~ clinical trial with a single therapeutic candidate ~~or medical device~~
- 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 continued clinical development of the therapeutic candidate
- Activities that support DEI goals described in the proposal
- Comparability studies
- Compilation of alternative comparator data acceptable to FDA for a marketing approval decision and intended to support the proposed interventional clinical trial in cases where placebo or sham controls are not possible. Examples include natural history studies or use of registries[1].
- Compilation of patient-reported outcomes (PRO) related to the conduct of the proposed trial[2]
- Compilation of real world data (RWD) and real world evidence (RWE) related to the conduct of the proposed trial[3]

[1] Applicants must have documented concurrence from FDA on the acceptability of the proposed comparator

[2] Compilation of PRO in the proposed trial must comply with FDA guidelines on Patient-Focused Drug Development [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-collecting-comprehensive-and-representative-input]

[3] Where relevant, CIRM encourages the use of RWD and RWE to support regulatory decision-making and recommends that applicants requesting funding for compilation of RWD and RWE consult with CIRM staff prior to submitting their application. Proposed use of RWD and RWE must comply with FDA guidances [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug].

CIRM funds 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 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.

ELIGIBILITY

What types of projects are eligible for funding?

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

(1) Must be ready to initiate work on the funded project within 45 days of approval

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

Because of the open and ongoing nature of this Program Announcement, investigators should only apply when their program has reached the stage where all eligibility criteria are met.

(2) Must propose a single clinical trial using a regenerative medicine-based therapy (stem cell-based or genetic therapy)

CIRM will support the completion 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[4] (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[5] approach (**i**) that targets a human somatic cell for its therapeutic effect; AND (**ii**) is intended to replace, regenerate, or repair the

[4] 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."

[5] 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.

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).

~~Device trials~~

~~Under an IDE, CIRM will support a feasibility trial of a medical device (including a diagnostic device), as follows:~~

- ~~A 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 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 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 and demonstrate appropriate stage of readiness to proceed with proposed trial

- ***All applicants*** must have an active IND~~/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).
- ***Phase 2 trial applicants*** must have Phase 1 safety data, obtained with the proposed candidate in an appropriate indication.
- ***Phase 3 trial applicants*** must have Phase 2 data for the proposed indication(s).

(4) Must include a project manager

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

(5) Must demonstrate appropriate level of co-funding

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" 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 Cost. 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 (e.g., copy of executed term sheet showing amount of co-funding, conditions, and source). 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 up to the award limit and must issue equity warrants to CIRM in order to cover the portion of the CIRM award amount that corresponds to the co-funding requirement.

Minimum Percentage of 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~~applicants or for-profit partners of non-profit applicants
    - 30% for for-profit partners of non-profit applicants
    - ~~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~~ applicants
    - 40% for for-profit partners of non-profit applicants

(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 intended IND~~/IDE~~ sponsor (i.e., the entity to be named as the sponsor on the IND ~~or IDE~~ application to the FDA) 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:

a. 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;

b. The applicant must have accounting systems in place that are capable of tracking CIRM funds; and

c. 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.

~~**(12) CIRM/NHLBI Cure Sickle Cell Disease Joint 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 Sharing policies and are required to share aggregate 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 Organization

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
- 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.

Who can serve as the Principal Investigator (PI)?

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

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

ADDITIONAL REQUIREMENTS

Diversity, Equity, and Inclusion (DEI) in CIRM-Funded Projects

All applicants for the CLIN2 program will be required to include a written plan in the application for outreach and study participation by underserved and disproportionately affected populations. In addition, applicants must provide a statement describing how the research team has considered the influence of race, ethnicity, sex, gender, and age diversity in the development of the proposed therapy or device. Applicants should discuss the limitations, advantages and/or challenges of developing a product or tool that addresses the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. Applicants should also address how the research team has or will incorporate diverse and inclusive perspectives and experience in the implementation of the research project, including, for example, developing partnerships with patient organizations, acquiring training in cultural competence and/or DEI, utilizing institutional resources for DEI, and allocating funds and/or personnel to address DEI.

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

Data Sharing 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.

SCHEDULE AND DEADLINES

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

REQUESTED FUNDING ALLOCATION

On an annual basis, CIRM will present for the Board's consideration a calendar-year budget for each of its on-going research programs, including the CLIN programs. The indirect cost rate will be set at 20% for non-profit applicant

organizations. CIRM will not fund indirect costs for for-profit applicant organizations.