RFA 13-03A: CIRM Strategic Partnership III Awards (Track A)

I. Purpose

The purpose of the Strategic Partnership Awards Initiative ("Initiative") is to attract industry engagement and investment in CIRM funded stem cell research. The intent of the Initiative is to create incentives and processes that will: (i) enhance the likelihood that CIRM funded projects will obtain funding for future clinical trials (e.g. follow-on financing), (ii) provide a source of co-funding for the earlier stages of clinical development, and (iii) enable CIRM funded projects to access expertise within pharmaceutical and large biotechnology partners in areas such as discovery, preclinical, regulatory, clinical trial design and manufacturing process development.

This Initiative requires applicants to show evidence of either having the financial capacity to move the project through development or of being able to attract the capital to do so. This may be evidenced by, for example, (i) significant investment by venture capital firms, large biotechnology or pharmaceutical companies, disease foundations and/or through the public markets; and financial statements evidencing significant liquid assets; or (ii) a collaborative research agreement with a large biotechnology or pharmaceutical company executed by two weeks prior to the review by the Application Review subcommittee of CIRM's Governing Board, the Independent Citizen's Oversight Committee (ICOC; Q2, 2014; exact date to be determined). These requirements are described further in Section V.D. The agreement with the large biotechnology or pharmaceutical company need only cover co-funding and collaboration support for the proposed project (and not future development).

CIRM intends to offer repeat calls under this initiative every 6-9 months. The focus, scope and objective may differ with each solicitation.

Award Tracks
Strategic Partnership III will have two possible Award tracks, Track A and Track B, as described below. Under this RFA, a for-profit applicant may apply through either Track A or Track B, but not both. Non-profit applicants may only apply under Track A.

Track A Awards (RFA 13-03A)
A Track A award will provide funding for a single development project for a single therapeutic candidate per applicant over a project period of up to 4 years. Under Track A, a non-profit Principal Investigator (PI) may submit a single application, and a for-profit organization may submit a single application.

Track B Awards (RFA 13-03B: Milestone Payment Pathway)
Track B awards will provide funding for up to five approved development projects per for-profit applicant organization, with funding contingent on successful achievement of the Major Development Milestone for each project, which will be agreed-to between CIRM and the applicant in advance of award issuance. Under Track B, a for-profit applicant organization may apply for funding for up to five different development projects, which may be focused on the development of different therapeutic candidates, or the use of a single therapeutic candidate to target distinct, non-overlapping disease indications.

Award Tracks A and B in RFA 13-03 are compared in Table 1:

Table 1: Features of RFA 13-03 Track A and Track B

Award Feature	RFA 13-03A (Track A)	RFA 13-03B (Track B)
Eligible Applicant Organizations	Not-for-Profit or For-Profit	For-Profit
Maximum Amount of Award Funding	Up to $10M* of **Total** Project Costs (including indirect & facilities costs)	Up to $10M of **Direct** Project Costs per Project
Co-funding Requirement	CIRM : Applicant = 1 to 1	CIRM : Applicant = 1.5 to 1
Number of Applications per Organization	1	Up to 5
Number of Applications per Principal Investigator	1	Up to 3
Readiness	Pre-IND Meeting Required (for Preclinical Stage Projects) or IND Filed (for Clinical Stage Projects) Before Application Deadline (October 21, 2013)	IND Filed Prior to Funding Approval (Q2, 2014)
Award Payment Schedule	Quarterly or Semi-annual Disbursements Throughout 4 Year Period of Award	Only upon Successful Achievement of Major Development Milestone
Commercial Validation Requirements to Demonstrate Financial Strength	Equity and/or Investment of $10M Over Previous 2 Years	Equity and/or Investment of $15M Over Previous 2 Years
Project Scope	IND-enabling Preclinical and Clinical Stage Activities	Clinical Stage Activities (including support activities such as manufacturing costs incurred during the project period)

* In certain extraordinary circumstances, a Track A award may be made up to $15M.

The specific details of <u>RFA 13-03A: TRACK A AWARDS are described below</u>. To apply for a Strategic Partnership Track B Award, refer to RFA 13-03B: TRACK B AWARDS.

RFA 13-03A: TRACK A AWARDS

II. Objectives and Scope

A. Objective

The objective of a Strategic Partnership III Track A award will be to achieve, in 4 years or less, the completion of a clinical trial under an Investigational New Drug (IND) application filed with the Food and Drug Administration (FDA).
Proposed projects will complete one or more of the following:

- A Phase 1 clinical study to demonstrate preliminary safety, assess measures of biological/clinical activity in humans, and determine a range of safe doses to be studied in subsequent trials.
- A Phase 2 clinical study to evaluate both safety and efficacy of the candidate therapy.

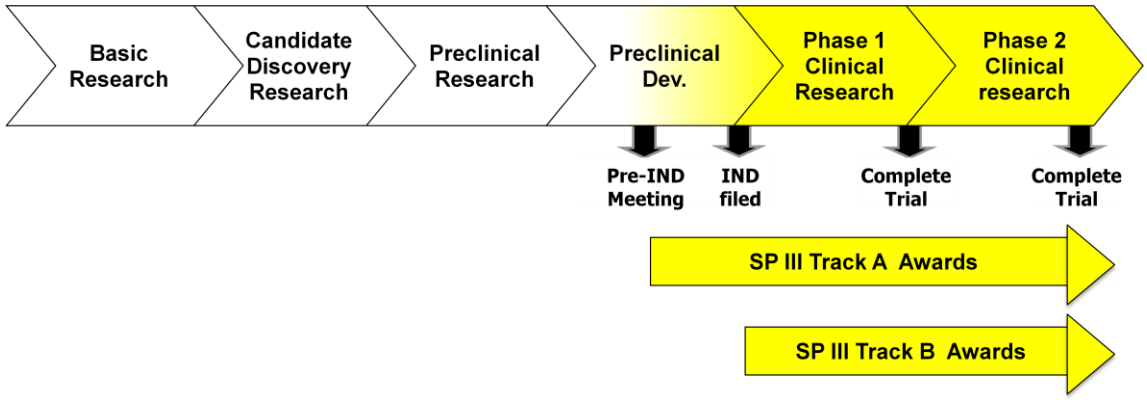
CIRM will only fund programs that include a clinical study that can be completed within the four-year project period. In RFA 13-03A, a clinical trial will be considered “complete” upon completion of enrollment, database lock and initial assessment of outcomes of the primary and secondary study objectives.

While all successful applicants are expected to complete a clinical trial within the four years of the award, the project can encompass IND-enabling as well as clinical research.

- For those projects beginning with IND-enabling studies, by the Letter of Intent (LOI) due date (August 22, 2013) the applicant must either have completed a pre-Investigational New Drug (pre-IND) meeting with the FDA or have a FDA-confirmed date for a pre-IND meeting that will take place prior to the application due date (October 21, 2013).
- For projects beginning with a clinical trial, the applicant must have filed a complete IND package with the FDA by the Application due date (October 21, 2013).

B. Scope

The scope of the Strategic Partnership III Awards (RFA 13-03A and RFA 13-03B) is illustrated in the figure below. Projects submitted under RFA 13-03A (Track A) can encompass IND-enabling as well as clinical research.



The key objective of a Strategic Partnership III **Track A** award is to complete a clinical trial. A RFA13-03A (Track A) award will support activities that meet this objective, including, but not limited to, the activities listed below:

- All activities necessary to initiate and complete an early clinical trial (Phase 1 or Phase 2) for a single therapeutic entity.
- IND-enabling activities necessary to enable a first-in-human clinical study proposed as part of the project.
- Supporting activities to enable the proposed clinical study such as cGMP production and/or further qualification/validation of relevant assays.
- Supporting studies performed in the context of the proposed trial that will provide critical additional data to better inform decisions on continued clinical testing. Applicants will be expected to justify how such studies will specifically inform the trial results and contribute to decision making.
- Process development activities necessary to enable further development of the therapeutic candidate such as optimization of cGMP production or development and validation of a potency assay.

In general, CIRM funding must be used to support research in California (see Section VIII.B.5 for a more detailed discussion of allowable uses of CIRM funding).

Research activities that fall outside the scope of this RFA include the following examples:

- Phase 3 clinical studies
- Early research and translation activities leading up to selection of a therapeutic development candidate
- cGMP production for Phase 3 studies
- Preclinical activities to enable removal of a clinical hold
- Non-interventional clinical studies (e.g. biomarker discovery; clinical studies not involving administration of the proposed therapy; or studies using samples not from subjects of the proposed clinical studies)
- Development and qualification of a medical device for the delivery of a product other than the product proposed in the funded project

C. Priority Areas

With respect to Track A applications, priority for the funding allotted for Strategic Partnership III will be given to eligible proposals that meet one of CIRM's priorities for RFA 13-03A (Track A), listed below:

- Proposals aimed at furthering the development of successfully completed CIRM-funded projects.
- Proposals from applicants that have secured a development agreement with a large biotechnology or pharmaceutical company committed to providing financial support for the proposed candidate.
- Proposals that include a Phase 1 or Phase 2 clinical study that could demonstrate clinical proof-of-concept in patients by the end of the project period, based on accepted endpoints of clinical efficacy or an acceptable biomarker relevant to the disease and predictive of clinical efficacy.
- Proposals that cannot, or are unlikely to, receive timely or sufficient federal funding.

In addition, special consideration will be given to applications previously submitted under a prior Strategic Partnership RFA that (i) meet the eligibility requirements of this RFA and (ii) have appropriately and satisfactorily addressed all of the comments of prior reviewers, as determined by the current Grants Working Group (GWG) reviewing the re-submitted application.

III. Award Information

A. Award

Under RFA 13-03, CIRM intends to commit up to $80M to support up to 8 development projects (in total) across both Track A (RFA 13-03A) and Track B (RFA 13-03B). Under Track A, CIRM will fund up to $10M of the total costs of a proposed project over four years or less (justifiable costs include direct project costs, facilities costs, and indirect costs). In *exceptional circumstances*, there is the potential to increase the award up to $15M per application, only if fully justified, and subject to approval by the Application Review Subcommittee of CIRM's Governing Board, the Independent Citizens' Oversight Committee (ICOC). For all proposals, co-funding is required (see Section III.B). The application must include a fully justified, detailed, activity-based budget which identifies activities that CIRM will fund and those that the applicant will fund.

B. Co-Funding

Under a RFA13-03A award, CIRM will require co-funding from the applicant, which may come from the applicant's own assets, from an industry partner, or from another funding source arranged by the applicant. Applicants must match 100% of the total CIRM funding requested (i.e. 1 to 1 match). In their application, applicants will be required to address the status and sources of co-funding required for achievement of the RFA objective. Applicant co-funding may be provided in the form of capital or justifiable in-kind services.

C. Budgets, Milestones and CIRM Oversight

For all RFA13-03A awards, CIRM reserves the right to negotiate funded project activities, milestones (both technical and financial), success criteria, timelines and budgets prior to issuance of the Notice of Grant Award (NGA) or Notice of Loan Award (NLA). In addition, CIRM will work with the PI to ensure that the team includes the necessary project management expertise, and reserves the right to approve the selection of a project manager. Progress in translational research is important to CIRM. Continued funding is contingent upon timely progress, as outlined in the project milestones and timeline established under the NGA or NLA, and the on-going ability of the applicant to fund its operations and to satisfy its co-funding commitment; continued funding decisions will also take into consideration competitiveness of the candidate therapy and the feasibility of subsequent development. CIRM reserves the right to terminate the project or to negotiate new milestones to refocus/redirect the project if agreed to milestones are not achieved, or if there are significant changes in the competitive landscape or feasibility of the development program.

The Grants Administration Policy (GAP; see Section XI.A) requires that the grant or loan recipient submit annual Progress Reports to CIRM and provide

notification of any serious adverse event related to the therapeutic candidate in a clinical trial. In addition, communication and reporting responsibilities of the grant or loan recipient to CIRM will include: 1) quarterly updates; 2) routine communication by the Principal Investigator (PI) or Project Manager; 3) discussion with CIRM's Clinical Development Advisory Panel (CDAP) at key decision points such as the transition from IND filing to initiation of a clinical trial; 4) receipt of key regulatory documentation such as the pre-IND briefing package, formal minutes from agency meetings or other key agency correspondence and 5) participation of CIRM representatives as observers in key regulatory meetings.

D. Covered Clinical Trial Costs

CIRM requires any clinical trial proposed for funding to include at least one clinical trial site in California. Only applicants that have demonstrated a sufficient presence in California (as described in Section V.C) are eligible for funding. Expenditures may include costs of clinical trials conducted outside of California as part of the funded project; see Section VIII.B.5 for further explanation of permissible expenses. CIRM expects funded clinical trials to include women and members of minority groups unless a clear and compelling rationale and justification establishes to the satisfaction of CIRM, that such inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

E. Sub-Contracts

CIRM has the option to review (for compliance with CIRM's policies and regulations and the advancement of its mission) contract/agreements (e.g. including, but not limited to, those with Contract Research Organizations (CROs) or Contract Manufacturing Organizations (CMOs)) which it deems critical to the success of the project. Upon request, the awardee will be required to provide such documentation.

F. Commencement/Other CIRM Awards

Given the urgency of CIRM's mission, all approved applications must be initiated (award start date in issued and signed NGA or NLA) within 6 months of approval and authorization for funding by the Application Review Subcommittee of the ICOC, unless CIRM's President grants an extension based upon compelling justification of the need for additional time. In the case of awards to applicants that already have a CIRM award such as a Disease Team I award, any funding disbursed to the applicant under this RFA will be for activities not funded by the already existing award.

IV. Award Mechanism

CIRM expects to fund approved proposals through grants or loans. Track A awards to non-profit organizations will be in the form of a grant. For-profit applicants may choose to accept the award in the form of a grant or a loan.

Grants under Track A are funded through quarterly or semi-annual disbursements (at CIRM's option) and are subject to the revenue sharing provisions in CIRM's regulations (Intellectual Property and Revenue Sharing Requirements for Non-Profit and For-Profit Grantees (17 Cal. Code Regs. § 100600 et seq.). It should be noted that an amendment to 17 Cal. Code Regs. section 100608(b) is currently pending with such proposed amendment available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

Loan recipients shall be governed by the CIRM Loan Administration Policy (LAP) that is in effect as of the date of the execution of the NLA. Approved applicants who accept a loan will pay for loan administration costs and the costs of CIRM's due diligence review out of funds included in the award. Loan applicants will be required to submit financial information in connection with CIRM's due diligence.

The terms of the Loan are set forth in detail in Appendix A. Applicants should be advised that with respect to any and all RFAs, the IP and Industry Subcommittee of CIRM's board may elect to adopt terms other than the guidelines set forth in the LAP. For additional information on the loan program, consult the CIRM LAP, available at: http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

V. Eligibility

For an **investigator-sponsored IND**, the investigator-sponsor must be the PI on the CIRM application.

For an **organization-sponsored IND**, the organization sponsor must be the applicant organization on the CIRM application, and the PI must be an employee of the applicant organization.

A. Project Eligibility

A proposal previously reviewed under a prior Strategic Partnership RFA may be submitted provided that the eligibility requirements of RFA13-03A (Track A) are met.

1. Project Objective: The proposed project must address a serious unmet medical need/injury and must include the completion, in 4 years or less, of a Phase 1 or Phase 2 clinical trial under an Investigational New Drug (IND) application filed with the Food and Drug Administration (FDA). The proposed clinical trial(s) will evaluate preliminary safety and assess measures of preliminary biological activity/efficacy in humans.

2. Therapeutic Candidate: Each proposed project must be focused on a single therapeutic candidate (that is, or will be, the subject of a single IND filing) that meets any of the following criteria:

    - a cell therapy derived from pluripotent stem cells
    - allogeneic tissue-derived stem cells or progenitor cells for repair/regeneration
    - stem cell-engineered functional tissues for implantation in vivo
    - a small molecule or biologic demonstrated to target normal endogenous stem cells in vivo as the primary mechanism of action (MOA) for repair/regeneration
    - a small molecule or biologic demonstrated to specifically target cancer stem cells as the primary MOA and for which there is compelling evidence for such activity, based on serial clonal transplantation assays in an in vivo model
    - genetically or pharmacologically-modified hematopoietic stem cells (HSCs; includes autologous or allogeneic approaches)

    Therapeutic candidates that fall outside the scope of this RFA include the following:
    - unmodified HSCs
    - small molecules and biologics, unless specifically targeting endogenous stem cells for repair/regeneration or cancer stem cells as the primary MOA
    - autologous mesenchymal stem cell (MSC) approaches
    - autologous tissue-derived stem cell approaches
    - minimally manipulated bone-marrow or minimally manipulated cord-blood

3. Readiness: The Strategic Partnership III RFA 13-03A is designed to capture mature development projects that are at or near an early clinical research stage.

Eligible projects for RFA 13-03A (Track A) will meet the following criteria:

- A single final therapeutic development candidate has been chosen, for which there is strong scientific and clinical rationale.
- Strong preclinical proof-of-concept (POC) evidence exists to support use of the candidate in the target disease/injury (for example, reproducible evidence of disease modifying activity in a relevant animal model using the intended therapeutic candidate).
- For projects proposing to start with IND-enabling studies, by the LOI deadline (August 22, 2013) the applicant must have completed a pre-IND meeting with the FDA or have an FDA-confirmed date for a pre-IND meeting that will take place prior to the application deadline (October 21, 2013). Based on the outcome of that discussion, a project should be projected to be within 12-18 months of IND filing.
- For projects ready to start a Phase 1 clinical trial, applicants must have submitted an IND package to the FDA by the application deadline (October 21, 2013). Any clinical hold issues not resolved at the time of application (October 21, 2013) should be projected to be resolved by the time of funding.
- For projects ready to start a Phase 2 clinical trial, applicants must have Phase 1 data demonstrating preliminary safety in the target population, by the application due date (October 21, 2013).

4. Commercial Validation: In addition, applicants must provide **Evidence of Commercial Validation** (Section V.D).

B. Institutional Eligibility

Applicant organizations must demonstrate a sufficient presence in California (as described in Section V.C) to be eligible for funding. All applicants must also provide evidence of commercial validation to be eligible for this award (Section V.D). Both non-profit and for-profit organizations may apply for a Track A award under RFA 13-03A.

"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. "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 are also referred to as "commercial organizations".

A for-profit applicant organization may submit only one application to RFA 13-03A (Track A). For-profit applicant organizations that hold 2 or more of the following awards: Disease Team, Disease Team Therapy Development, or Strategic Partnership, as of the application due date, October 21, 2013, are not eligible to apply for this award.

C. California Presence

By the Application Date (October 21, 2013): If the applicant organization does not already have operations located in California, it must have a lease or ownership of a location from which the project will be performed, or a letter of intent or term sheet demonstrating that the applicant is engaged in negotiations to secure a specified location in California from which location it will engage in activities critical to the project.

In addition, the applicant must show the following ties to California:

1. To qualify for any CIRM funding, an applicant organization must have at least 2 full-time equivalent (FTE) non-administrative employees in California during the project period. In addition, the PI is expected to spend at least 30% time in California, working on the approved project. Thus, at a minimum, each applicant organization is required to have at least 2.3 FTEs (0.3 of which represents the PI) located in the state of California during the project period.

2. In addition to the minimum requirement of 2.3 FTEs in California, as described in Section V.C.1, for applicant organizations having greater than 30 employees world-wide, the following requirements apply:

   (i) For applicant organizations which have, within 6 months of the start of the CIRM funded project, at least an additional 5% of the applicant organization's workforce (FTE, up to a maximum of 50 employees) located in California during the project period, the applicant organization would be eligible to use its approved CIRM funding for clinical trial costs and non-research costs incurred both within and outside the State of California, as permitted by CIRM's regulations and RFA13-03A.

   (ii) For applicant organizations which do not satisfy the requirements of subparagraph (i), above, the organization must spend 100% of its approved CIRM funding in California.

   Failure to adhere to these requirements will result in a penalty and possible termination of the funding commitment.

D. Evidence of Commercial Validation

In order to attract projects having or likely to attract industry investment, including follow-on financing of Phase 3 clinical trials, or having adequate self-funding, applicants must provide evidence of commercial validation as part of the submitted application. Such evidence will require submission of supporting documentation, satisfying at least one of the following:

1. Financial Strength and Historical Investment:
   The applicant is a for-profit that has (a) obtained in the past two years, an equity and/or programmatic investment through the public markets or by venture capital firms, large biotechnology or pharmaceutical companies (market capitalization of at least $500M), non-profit foundations or government entities, in the amount of at least $10M **AND** (b) at least one year of balance sheet cash (as demonstrated by its most recent financial statements and pro-forma for any concurrent investment) based on the last twelve months (LTM) operating cash burn rate, without taking into account any funds provided by CIRM, but including the first 12 months of co-funding to be provided by the applicant if awarded the CIRM grant or loan. For purposes of RFA 13-03A, LTM operating cash burn is defined as cash flow from operations, less capital expenditures and any debt service.

AND/OR

2. Agreement with a Biopharmaceutical Partner:
   If the applicant is a non-profit or a for-profit that is seeking to establish commercial validation by virtue of a collaborative research agreement with a large biotechnology or pharmaceutical company having a market capitalization of at least $500M to provide the financial and/or in-kind support for the match required by RFA 13-03A, the applicant should submit a fully executed copy of such agreement if one already exists. If such an agreement has not yet been entered into, by the date of the LOI (August 22, 2013) the applicant must provide a letter from the biotechnology or pharmaceutical company indicating its interest in co-funding the proposed project and that the parties are negotiating the terms of support. The applicant must submit a term sheet and/or letter of intent relating to such agreement, signed by the partner, by the date that Supplemental Information must be filed (January 6, 2014) and a fully executed agreement must be provided by two weeks prior to the date of the ICOC/Application Review Subcommittee meeting to approve and authorize funding for Strategic Partnership III awards (Q2, 2014; exact date to be determined).

See Section VIII.A for specifics of documentation required as part of the LOI and Application. **The agreement with the large biotechnology or pharmaceutical company** need only cover co-funding and collaboration support for the proposed project (and not future development). To that end, the agreement can be in the form of an option, license, funded research collaboration or sponsored research agreement, as long as it provides for a level of co-funding and/or in-kind services sufficient to permit the applicant to meet its co-funding obligations.

If CIRM determines that these requirements are not met, it may terminate all further action on the application.

E. Principal Investigator (PI) Eligibility

CIRM requires that a single PI and a single applicant organization (the PI's organization) be designated in a RFA 13-03A (Track A) application. The PI is the designated point of contact for CIRM and is the person responsible and accountable to CIRM for scientific performance on the project. The applicant organization is the designated contact institution for all financial and other administrative considerations.

The PI must have an M.D., Ph.D. or equivalent degree and must be authorized by the applicant organization to conduct the proposed research in California. By the application deadline, the PI must:

- Be an employee of the applicant organization who commits at least 30 percent time working on the project out of the California office of the applicant organization, and have demonstrated expertise in drug development and in managing clinical research programs.
- Have documented authority from the applicant organization to staff the proposed project in California.
- Have documented commitment from the applicant organization to provide resources sufficient to carry out the proposed research.

In order to ensure effective leadership of this development stage program, CIRM is limiting the number of active CIRM Disease Team, Disease Team Therapy Development, or Strategic Partnership awards in which an investigator may participate as a PI or a Co-PI. Unless the proposed project is a *continuation* of a previous CIRM-funded Disease Team or Disease Team Therapy Development project, RFA13-03 is not open to investigators who are already a PI or a Co-PI on an active CIRM Disease Team, Disease Team Therapy Development or Strategic Partnership award as of October 21, 2013, the deadline for submission of the full application.

In addition, in order to broaden the pool of applicants engaged in stem cell research and to encourage leveraging of CIRM's investment, CIRM is limiting the number of *overall* active CIRM research awards in which an investigator may participate as PI or Co-PI. RFA 13-03 is not open to investigators who are already a PI or Co-PI on 3 or more active CIRM awards as of October 21, 2013, the deadline for submission of the full application. The limit includes all CIRM awards that have been approved but not yet closed out, with the exception of the following CIRM RFAs: Shared Research Labs, Major Facilities, Research Training Awards I & II, Bridges to Stem Cell Research, or Conference Grants.

F. Project Manager Eligibility

CIRM requires a project management professional (Project Manager) be designated in each RFA 13-03A (Track A) Award application. The Project Manager must have relevant experience in managing preclinical and clinical development programs and must be able to devote an appropriate (≥50%) percentage effort, in California, to the project.

G. Extraordinary Exceptions

In extraordinary circumstances, the President has the discretion to permit exceptions to requirements or limitations in Sections V and VIIIA. The exercise of such discretion will be only in exceptional cases where the applicant has demonstrated that such an exemption would preserve an important research opportunity or make a critical contribution to one of CIRM's mission objectives. Exceptions must be consistent with the objectives of this RFA and the requirements of Proposition 71 as well as California state regulations, including the Grants Administration Policy (GAP; Section XI.A) and the Loan Administration Policy (LAP; Appendix A), or they will not be considered. Exceptions may include permitting the disbursement of initial funding while an out-of-state company is in the process of building its operation in California, upon a showing of a good faith effort to adhere to the requirements above and upon terms and conditions which will be imposed pursuant to such exception.

If CIRM determines that an application does not meet the eligibility requirements, CIRM may terminate all further action on the application. Applicants who will need an exception must request it at least 14 days before the LOI deadline or at least 30 days before the relevant application deadline. To request an exception, or for assistance in determining whether one is necessary, contact the CIRM staff listed in Section X.

VI. Application and Evaluation Processes

Submission of an application for a Strategic Partnership III Track A Award (RFA 13-03A) involves a two-step process. An eligible applicant (see Section V for eligibility criteria) must first submit a Letter of Intent (LOI). Applicants will be notified if their LOI is **NOT** accepted.

In the second step of the process, eligible applicants will submit a full application. Applications will only be accepted from applicants that meet all eligibility requirements and have submitted an LOI that was accepted by CIRM.

A. Application Review Process

Applications for the CIRM Strategic Partnership III Awards will be evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board (ICOC), and the Chair of the Governing Board. 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 review the applications and score them according to scientific and technical merit applying the review criteria described in Section VII. The entire GWG will make funding recommendations based on scientific merit. The Board's Application Review Subcommittee will make funding decisions based on the GWG recommendations, any staff recommendations and a programmatic review.

CIRM's priorities for RFA 13-03A (Track A) include:

- Proposals aimed at furthering the development of successfully completed CIRM-funded projects.
- Proposals from applicants that have secured a development agreement with a large biotechnology or pharmaceutical company committed to providing financial support for further development of the proposed candidate if milestones are met.
- Proposals that include a Phase 1 or Phase 2 clinical study that could demonstrate clinical proof-of-concept in patients by the end of the project period, based on accepted endpoints of clinical efficacy or an acceptable biomarker relevant to the disease and predictive of clinical efficacy.
- Proposals that cannot, or are unlikely to, receive timely or sufficient federal funding.

In addition, special consideration will be given to applications previously submitted under a prior Strategic Partnership RFA that (i) meet the eligibility requirements of this RFA and (ii) have appropriately and satisfactorily addressed all of the comments of prior reviewers as determined by the current GWG reviewing the re-submitted application.

B. Project Evaluation Process

Project progress for all successful awardees from RFA 13-03A (Track A) will be evaluated by a group of external experts, the Clinical Development Advisory Panel (CDAP), either annually, or at key milestones and decision points such as the transition from IND filing to initiation of a clinical trial.

CIRM's confidentiality and conflict screening rules will apply to everyone who will have access to applications or who will attend the review meeting, including CIRM staff and external reviewers and members of the CDAP. (Per Gov. Code §6254.5(e) non-public records may be disclosed to government agencies under confidentiality agreements). The policies, procedures and laws that address confidentiality of records submitted to CIRM are described in Section XII.

VII. Review Criteria

Applications for RFA 13-03A (Track A) will be evaluated for scientific merit by the GWG in five key areas: 1) Significance and Impact; 2) Scientific Rationale and Risk/Benefit; 3) Design and Feasibility; 4) Principal Investigator, Development Team and Leadership Plan; and 5) Quality of Collaborations, Assets, Resources and Environment. The specific criteria for review of applications are based on the standard review criteria described in the CIRM GAP (Section XI.A).

The GWG will be asked to give special consideration to CIRM's priorities for this RFA (Section VI).

For projects that have undergone a due diligence analysis by a pharmaceutical/biotechnology partner resulting in an executed development agreement or a term sheet or letter of intent to enter into a development agreement, reviewers are asked to assess the thoroughness of the diligence analysis with respect to evaluation of Clinical Competiveness and Impact, Scientific Rationale and Risk Benefit, and Design and Feasibility, as set forth below, and to appropriately weigh both the scope of the investigation and its conclusions in their scientific scoring.

A. Significance and Impact

1. Target Product Profile: Evaluate whether the target product profile (TPP) conveys the long term aspirational product attributes and overall intent of the development program and contains metrics for key attributes to enable decision making.

2. Clinical Competitiveness and Impact: Where a due diligence investigation has been conducted in regard to the proposed therapeutic, assess if the investigation was thorough in evaluating the potential for a competitive

product. Otherwise, evaluate whether the proposed therapeutic candidate could have a significant impact on the target disease/injury and if it would offer clinically meaningful advantages over current therapies on the market or in late stage development. Assess if the proposed project could advance the field of stem cell-based/regenerative medicine.

3. Responsiveness**:** Determine if the proposed therapeutic candidate convincingly uses or targets stem cells. Evaluate whether the proposed activities are within scope as defined in Section II. Evaluate if this is a project that should receive priority as stated in Sections II and VI.

B. Scientific Rationale and Risk/Benefit

Where a potential or existing partner has conducted a due diligence investigation on rationale and risk benefit for the proposed therapeutic, assess whether the investigation was thorough. Otherwise, assess if there is strong scientific rationale and a favorable risk/benefit ratio for the proposed therapeutic intervention in the target disease/injury. Based on the preclinical data and any available clinical data, is there a reasonable expectation that the proposed therapeutic approach will have a meaningful clinical benefit for patients and are the potential risks to subjects manageable and acceptable in the context of the target patient population?

C. Design and Feasibility

Where a potential or existing partner has conducted a due diligence investigation regarding the proposed project plan and key components, assess whether the diligence investigation was thorough. Otherwise, assess the following**:**

1. Development Plan to End-of-Phase 2: ("End-of-Phase 2" is defined here as completion of early clinical studies providing sufficient information on safety, efficacy, dose and dosing regimen, to enable the transition to Phase 3. The Project Plan described below may overlap completely with the Development Plan to End-of-Phase 2, or may comprise a subset of that plan).

   Under this RFA, proposed projects are expected to include a well thought out development plan to End-of-Phase 2 that is realizable, is designed to enable the transition to Phase 3, and supports achievement of the Target Product Profile. Evaluate if the proposed plan meets these criteria.

2. Project Plan: The Project Plan describes the scope of work that will be conducted during the award period and can overlap wholly, or in part, with the above Development Plan. Evaluate the design and feasibility of the Project Plan with respect to the following:

    - Is the proposed project integral to the Development Plan to End-of-Phase 2?
    - Is the overall Project Plan feasible and could it meet the objective of RFA 13-03A (Track A), which is to complete a clinical trial within the project period?
    - Is the clinical operations plan adequate to support successful execution and oversight of the clinical trial?
    - Do the project milestones capture key activities and are they reliable indicators of the project's progress?
    - Are the criteria for Go/No Go decisions adequately defined?
    - Is the project timeline realistic and achievable?

3. Key Project Components: Assess the proposed project with respect to the following:

    a. Feasibility of the *Preclinical Plan*:
        - If the project proposes starting with IND-enabling studies, is the IND-enabling plan adequate to enable regulatory approval to advance to a clinical trial?
        - Based on the outcome of the pre-IND meeting with FDA, is it feasible to project filing of the IND within 12-18 months of the funding start date (earliest funding expected Q3, 2014)?

    b. Feasibility of the *Regulatory Path*:
        - Are major issues that were raised during the pre-IND meeting being addressed?
        - If the project proposes starting with a clinical trial but is on clinical hold, is it feasible to expect that all clinical hold issues will be addressed by the time of funding (i.e. within 6 months of approval for funding by the ICOC/Application Review Subcommittee in Q2, 2014)?

    c. Feasibility of the *Manufacturing Strategy*:
        - Is the manufacturing strategy feasible to supply the proposed clinical trial and are mitigation strategies appropriate to address manufacturing bottlenecks?
        - Will the manufacturing process support scale up for future larger trials and commercialization?
        - Are there steps in the manufacturing process that could adversely impact clinical adoption?

d. Design and Feasibility of the Proposed *Clinical Study*:
   - It is expected that any clinical trial proposed for funding under RFA 13-03A will be designed to inform decisions on further development of the candidate therapy and to inform the design of subsequent clinical trials. Are these criteria met?
   - Is the proposed study well-designed and likely to achieve the RFA objectives of evaluating both preliminary safety and assessing measures of biological activity/efficacy in humans?
   - Is the trial designed to test or elucidate mechanism(s) of action of the therapeutic such that, regardless of clinical outcome, information will be gained?
   - Is the choice of patient population appropriate?
   - Are enrollment projections realistic and can they likely be completed during the award period?
   - Are appropriate mitigation strategies in place to address delayed enrollment?

D. Principal Investigator (PI), Development Team and Leadership Plan

Assess the proposed project with respect to the following:

1. Expertise and Track Record of PI: Does the PI have relevant experience in therapy development and demonstrated successful leadership experience, and will the PI play a key role in the proposed project?

2. Development Team and Leadership Plan: Has an appropriate multidisciplinary team been assembled to execute the project? Does the team include a Product Development Lead, CMC Lead, Preclinical Lead, Clinical Lead, and a Regulatory Lead in addition to the required Project Manager? Do these team leads have demonstrated expertise in their functional area? Has the PI developed a leadership and communication plan that will ensure successful execution of the project? Does the plan include methods for progress monitoring, project decision-making and conflict resolution?

3. Clinical Investigators at Clinical Sites: Do the lead clinical investigators have relevant experience in the target disease area and in conducting clinical studies?

4. Budget: Is the proposed budget, both overall and for key activities, appropriate and well justified? Are projected costs for key activities (such as IND-enabling activities, CMC activities, clinical trials) reasonable, adequately presented and sufficiently detailed?

E. Collaborations, Assets, Resources and Environment

Assess the proposed project with respect to the following:

1. Collaborations: Are collaborations in place (including those with a co-funding partner) that will be needed for the success of the project?

2. Clinical Sites: Are the proposed clinical sites experienced in conducting Phase 1 and Phase 2 trials? Are the proposed clinical sites sufficiently likely to enroll patients for completion of the trial within the 4 year project period?

3. Assets: Are there sufficient assets, specifically intellectual property (IP) and/or licenses available to the project? Does the project have critical IP, Material Transfer Agreements (MTAs) or license agreements necessary to enable development of the therapeutic candidate, either already in place or at an adequate stage of negotiation to enable both the development program and future commercialization of the proposed product (see Section VIII.B, Part J)? Do the applicants have agreements in place to cross-reference Drug, Device or Facility Master File(s) submitted by the industry partner/collaborator with the appropriate section(s) of the FDA (see Section VIII.B, Part I)?

4. Contract Services: Do the proposed CROs/CMOs/consultants have the experience and expertise necessary to successfully meet expectations, deliverables and timelines? Does the development team have appropriate oversight expertise?

5. Resources and Environment: Are the necessary facilities, major equipment, and services available for conducting the proposed research?

VIII. Application Procedure

Applicants must follow these instructions for submission of a Letter of Intent (LOI) and a Strategic Partnership III Track A award application (RFA 13-03A). Applicants will be notified if their LOI was **NOT** accepted.

Applications will only be accepted from PIs who submitted a LOI that was accepted by CIRM. The PI and the project proposed in the application must be the same as those described in the LOI; otherwise, the application is deemed ineligible.

A. Letter of Intent (LOI) and Commercial Validation

A PI may submit only a single LOI for this RFA using the forms and instructions provided in the Grants Management Portal at https://grants.cirm.ca.gov. The LOI should concisely describe the proposed project and explain how it will, within four years, achieve the objective of the RFA13-03A (Track A), which is to complete a Phase 1 or Phase 2 clinical trial. Documentation in support of commercial validation is required as part of the LOI submission. See below and refer to the LOI instructions and form.

Commercial Validation

Evidence of Commercial Validation must be provided as part of the LOI submission and consists of the following.

1. **If the applicant organization is a for-profit** and is seeking to establish commercial validation through demonstration of financial strength and historical investment (see Section V.D.1), provide documentation showing that the applicant has:
   (a) obtained in the past two years, an equity and/or programmatic investment through the public markets or by venture capital firms, large biotechnology or pharmaceutical companies, non-profit foundations or government entities in the amount of at least $10M **AND**
   (b) at least one year of balance sheet cash (as demonstrated by its most recent financial statements and pro-forma for any concurrent investment) based on the last twelve months (LTM) operating cash burn rate, without taking into account any funds provided by CIRM, but including the first 12 months of the applicant's co-funding obligation **AND**
   (c) For purposes of RFA 13-03A, LTM operating cash burn is defined as cash flow from operations, less capital expenditures and any debt service.

   Specific documents that should be provided are:
   - Financial statements prepared in accordance with US GAAP for the quarters ended June 30, 2012 and June 30, 2013, as well as year ended December 31, 2012.
   - Documents sufficient to establish the amount invested by venture capital firms, large biotechnology or pharmaceutical companies and/or non-profit foundations, including supporting data such as a capitalization table, to demonstrate $10M in prior investment. When available, (even if subsequent to the LOI deadline), applicant will provide financial statements prepared in accordance with US GAAP for the year ended December 31, 2013.

AND/OR

2. **If the applicant is a non-profit or a for-profit** and is seeking to establish commercial validation by virtue of an agreement with a large biotechnology or pharmaceutical company having a market capitalization of at least $500M (see Section V.D.2) to provide the financial and/or in-kind support for the match required by RFA 13-03A, the applicant should submit a fully executed copy of such agreement if one already exists. If such an agreement has not yet been entered into, by the date of the LOI (August 22, 2013) the applicant must provide a letter from the biotechnology or pharmaceutical company indicating its interest in co-funding the proposed project and that the parties are negotiating the terms of support. The applicant must submit a term sheet and/or letter of intent relating to such agreement, signed by the partner, by the date that Supplemental Information must be filed (January 6, 2014) and a fully executed agreement must be provided by two weeks prior to the date of the ICOC/Application Review Subcommittee meeting to approve and authorize funding for Strategic Partnership III awards (Q2, 2014; exact date to be determined).

   A term sheet or letter of intent relating to the agreement should address the following:
   - Levels of co-funding for the proposed project (need not include future development) which the applicant, with its biopharmaceutical partner, agrees to on an annual basis and the amount it is requesting CIRM to fund annually.
   - A general description of the agreement structure with the biotechnology or industry partner (e.g. option agreement, licensing agreement with rights of termination, opt-ins, or opt-outs, etc.).
   - All payments the applicant would receive including upfront payments, any research and development support, FTE support, and milestone payments.
   - The amount, nature and value of in-kind services, including but not limited to FTEs, that an industry partner will provide without charge, such as experience in regulatory affairs, process development or clinical development.

The completed LOI and supporting evidence of commercial validation, must be submitted online using the CIRM Grants Management Portal at https://grants.cirm.ca.gov and must be received by CIRM no later than 5:00 PM (PDT) on August 22, 2013. No exceptions will be made.

B. Application Forms

A PI may submit only a single application for RFA 13-03A (Track A), corresponding to the accepted LOI, using the forms and instructions provided in the Grants Management Portal at https://grants.cirm.ca.gov. Application forms for this RFA will be available in August/September, 2013.

The application for RFA 13-03A consists of up to **ten parts**:

Part A: Application Information Form (Web-based form). Includes Abstract, Public Abstract, Statement of Benefit to California, Key Personnel, Budget, Budget Justification and Related Business Entities Disclosure (additional details in sections number 1- 6, below).

Part B: Strategic Partnership III Track A Award Proposal (MS Word template). Includes Target Product Profile; Clinical Competitiveness and Impact; Scientific Rationale and Risk/Benefit, Development Plan to End-of-Phase 2, Project Plan with Milestones and Timeline; IND Status; Clinical Protocol Synopsis; Manufacturing Plan Synopsis; PI, Development Team and Leadership Plan; Collaborations, Assets, Resources and Environment; Clinical Sites; Intellectual Property, Licenses and Agreements; References (additional details in sections number 7-19, below).

Part C: Biographical Sketches for Key Personnel (MS Word template). Includes key clinical investigators and letters of collaboration and/or institutional support.

Part D: Due Diligence Report. For projects that have undergone a due diligence analysis by a pharmaceutical/biotechnology partner resulting in an executed agreement or a term sheet or letter of intent to enter into an agreement, provide a summary and/or checklist of the due diligence investigation (additional details in section number 20, below).

Part E: Activity Based Budget

Part F: FDA Correspondence. Copies of regulatory correspondence with the FDA must be provided.

Part G: Clinical Protocol. Required for projects that propose conducting a clinical trial. If final is not available, submit draft.

Part H: Investigator Brochure. Required for projects that propose conducting a clinical trial. If final is not available, submit draft (additional details in section number 21, below).

Part I: Copies of Authorization for Cross Reference of Drug, Device or Facility Master Files

Part J: Licenses and agreements (MTAs). If you have licenses or MTAs in place, submit copies.

The Application includes the following sections:

1. Abstract *(divided in four parts of up to 3000 characters each; in Part A)*

Part 1. Project Description: Briefly describe the proposed therapeutic candidate and summarize the scientific rationale for the proposed intervention in the target disease/injury.

Part 2. Clinical Competitiveness and Impact: Describe the unmet medical need that the proposed therapy will address and explain how the proposed therapy could improve patient care compared to other therapies either available or in development.

Part 3. Proposal Overview: Summarize the proposed project plan and describe how it will (a) achieve the overall objectives of the Strategic Partnership Program, which is to leverage CIRM funding and the potential to provide follow-on funding to bring therapies through development and (b) achieve the specific objective of RFA 13-03A, which is to complete a clinical study within the 4 year project period.

Part 4. Milestones: Summarize high level milestones to be achieved within the 4 year award period.

2. Public Abstract *(up to 3000 characters; in Part A)*
In lay language, briefly describe the proposed project and explain how the proposed stem cell-derived therapy will advance the treatment of disease or serious injury in humans. This Public Abstract will become public information and will be available online; do not include proprietary or confidential information, or information that could identify the applicant and applicant organization or, if applicable, the biopharmaceutical partner.

3. Statement of Benefit to California *(up to 3000 characters; in Part A)*
Describe in a few sentences how the proposed research will benefit the State of California and its citizens. This Statement of Benefit will become public information and will be available online; therefore, do not include proprietary or confidential information or information that could identify applicant and/or biopharmaceutical partner (e.g., PI name, applicant institution name or location).

4. Key Personnel *(included in Parts A and C)*
List all key personnel and their roles on the project in the relevant sections of Part A. Key personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive way, whether or not they receive salaries or compensation under the grant. Key personnel may include any staff, collaborators, or consultants who meet this definition. Key personnel who are not part of the applicant organization should be listed in the subcontract section of the application. For example, list the key lead investigator for each clinical site even though he/she will be compensated as part of a subcontract. It is not necessary to name other clinical site personnel who will be participating in the conduct of the study. Personnel that are not key, such as technical support staff, may be supported by award funds but not named. A minimum of one percent effort is required for each key person with the exception of the PI, who is required to commit a minimum of thirty percent (30%) effort, and the Project Manager, who is required to commit a minimum of fifty percent (50%) effort.

For each key person listed, provide a two-page biographical sketch using the template provided under Part C. The biographical sketch should highlight relevant experience, in particular, team leadership, conduct of clinical studies and/or contribution to regulatory filings for product development. Include relevant publications, patents or patent applications. Following the biosketch for the PI, provide biosketches for functional area heads and/or members of the development core team (including the individuals responsible for overseeing clinical, clinical operations, regulatory, CMC, data management and translational research activities) and for the lead clinical investigator at each proposed site. Thereafter, include all remaining biosketches in alphabetical order.

5. Budget *(included in Parts A and E)*
Provide all budget information requested in the budget section of Part A and in Part E. Specify and provide well-justified budgets for subcontracts and consultants in the appropriate section in Part A. In the activities-based budget spreadsheet (Part E), detail key activities and associated costs. Include costs proposed to be funded by CIRM through this award, funded through another CIRM award, or through co-funding either by self funding or through third parties. Proposed budgets should align with the sequence of when the activities will be conducted and must be well justified in the appropriate section of Part A. All allowable costs for research funded by CIRM are detailed in the CIRM GAP (Section XI.A).

Under RFA 13-03A, CIRM-funded allowable costs include the following:

- ***Salaries for Key Personnel and other Support Staff***
  Salaries for personnel may include the PI and key technical or other support staff, each of whom must perform the subject work in California,

based on percent of full time effort commensurate with the established salary structure of the applicant institution. The total salary requested must be based on a full-time, 12-month staff appointment or the full time annual salary for employees of a for-profit institution. Institutions may request stipend, health insurance and allowable tuition and fees as costs for trainees. Administrative support salaries for financial administration can be budgeted as direct project costs if adequately justified. All other administrative support salaries should be covered exclusively by allowed Indirect Costs.

- ***Supplies***

Grant funds will support supplies, including specialized reagents and animal costs. Minor equipment purchases (less than $5,000 per item) are considered supplies and may be included as direct costs in the budget.

- ***Travel***

Recipients (PIs) of a CIRM Strategic Partnership III Award are strongly encouraged to attend a CIRM-organized grantee meeting in California and will be required to attend Clinical Development Advisory Panel (CDAP) meetings in San Francisco at key milestones/decision points. Applicants should budget for one such meeting per year. Travel costs for these meetings should be included in the budget. Travel costs associated with collaborations necessary to the grant are allowable. Details of allowable travel costs can be found in the CIRM GAP (Section XI.A).

- ***Equipment***

Major equipment (more than $5,000 per item) necessary for conducting the proposed research at the applicant institution should be itemized and justified. Equipment costs should not be included as allowable direct costs in indirect cost calculations.

- ***Consultants/Subcontracts***

Grantees that subcontract CIRM-funded work should note that CIRM-funded research must generally be conducted in California. Examples of such research include study design; clinical protocol development; design of a toxicology study; analysis and interpretation of data; development of new methods.

Aside from small consulting contracts, Grantees may not use CIRM funds to contract for *research* to be performed outside of California. Consulting contracts for out-of-state research are limited to $15,000 per year for a single contract, and $25,000 per year in aggregate. (CIRM may allow modest increases to these limits in exceptional circumstances.)

Except as set forth in Section V.B, for activities other than research, Grantees may subcontract outside California, but must make a good faith

effort to use California suppliers for more than half of their contracts and purchases in accordance with CIRM's California Supplier regulation (Cal. Code Regs., tit. 17, § 100502). Examples of such activities include execution of a clinical trial according to a protocol, execution of a toxicology study performed according to an existing protocol and cGMP manufacturing. (Clinical trial execution would include blinding, randomization, patient recruitment, patient treatment, medical monitoring, data collection, clinical site selection/site initiation and Institutional Review Board (IRB) activities.)

For any clinical trial that is part of the proposed project, at least one of the clinical sites implementing the protocol must be in California.

- ***Facilities Costs***

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%. Facilities rates are applied to direct project costs exclusive of the costs of equipment, tuition and fees and subcontract amounts in excess of $25,000. Applicants may use lower Facilities rates, and use up to 100% of the awarded funds for direct research purposes. The Facilities cost rate budgeted is to be applied to the entire award project period.

- ***Indirect Costs***

Indirect costs are limited to 10% for for-profit applicants, and to 20% for not-for-profit applicants, 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, and subcontract amounts in excess of $25,000. Applicants may use lower indirect cost rates and use up to 100% of the awarded funds for direct research purposes. The Indirect cost rate budgeted is to be applied to the entire award project period.

6. Related Business Entities *(included in Part A)*

In order to comply with the Conflict of Interest policies under which CIRM operates, all applicants must provide information on related business entities for any application that, if awarded, would fund a for-profit organization either as: 1) the applicant organization; 2) a subcontractor or 3) the employer of a consultant or subcontractor. If the application does not seek funding for any such for-profit organizations, indicate that on Part K and submit the form. If for-profit funding is sought, include the following for each such for-profit organization to be funded:

- A list of any parent organization that owns 50% or more of the for-profit's voting shares;
- A list of all subsidiaries in which the for-profit owns 50% or more of the voting shares; and
- A list of all other related business entities (i.e., entities with which the for-profit shares management and control, or shares a controlling owner).

7. Target Product Profile *(up to 2 pages; use TPP template in Part B; also included as Sample C)*

Provide a target product profile (TPP) for the proposed therapeutic candidate. The TPP provides the aspirational attributes of the product to help define success and inform the proposed label. The TPP should articulate the overall intent of the therapeutic development program, and the studies proposed within this research proposal should be designed to collect data that will support the TPP. The TPP should provide the optimal profile (ideal) and the threshold profile (minimally acceptable to differentiate from current and future competing products), and identify criteria (metrics) for key decisions in the development process. It is a comprehensive outline of product specifications with respect to safety, effectiveness, quality, clinical evaluation, non-clinical evaluation, regulatory requirements and commercial factors e.g., market advantage and target differentiation. The TPP is a dynamic document that should be continually refined as data evolves and will ultimately become the product label.

Using the CIRM TPP template in Part B of the application (see Sample C for the template), provide the desired attributes/claims of the therapeutic for the following: indication, target activity, patient profile, efficacy endpoints, safety/contraindications, dose/regimen, dosage form and route of delivery. The FDA released the draft guidance document "Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool" which may be a helpful resource for developing a TPP. It is available from the FDA's website (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf). It is worth noting that while this document was developed and issued by the FDA's Center for Drug Evaluation and Research, it contains many guiding principles that apply to developing a TPP for cell therapies and biological products, as well as to products regulated by the Center for Drug Evaluation and Research (CDER).

8. Clinical Competitiveness and Impact *(up to 3 pages; in Part B)*
Summarize the current standard of care and competitive landscape for the target disease/injury. Describe how the proposed novel therapy could lead to a significant improvement in patient care compared to existing therapies or to other therapies currently in late-stage development. Describe the pharmacoeconomic rationale for the proposed therapeutic. Explain how the proposed project will advance the field of stem cell-based or regenerative medicine.

9. Scientific Rationale and Risk/Benefit *(up to 10 pages; in Part B)*
Describe the scientific rationale for the proposed therapeutic intervention. Summarize the evidence supporting use of the proposed therapeutic in the target disease and provide key data. Provide a summary (in tabular form) of the key preclinical and clinical (if available) safety and efficacy studies and summarize major outcomes and findings (you may reference appropriate sections of the Investigator Brochure).

Describe the potential benefits and risks of the proposed therapy and explain why the potential benefits outweigh the risks and justify use of the proposed therapeutic intervention in the target disease/injury. The Risk/Benefit analysis is based on the target patient population, other therapeutic options for that population, the scientific rationale, preclinical pharmacology and toxicology studies, and the therapeutic approach.

10. Development Plan to End-of-Phase 2 *(up to 3 pages; in Part B)*
Summarize the development plan to End-of-Phase 2 for the proposed therapeutic candidate and provide a high-level timeline highlighting key preclinical, clinical, CMC, regulatory and other milestones and major decision points, as well as costs to achieve these major milestones. As noted above (Section VII.C), “End-of-Phase 2” is defined as completion of early clinical studies providing sufficient information on safety, efficacy and dose, to enable the transition to Phase 3.

11. Project Plan, Milestones, and Timeline *(up to 8 pages plus 1 page for timeline, the latter in Gantt chart format or equivalent; in Part B)*

> ***Project Plan*****:** Describe the project plan and scope of activities proposed for funding under this award. Indicate activities to be conducted by the applicant and/or, if applicable, by the partner. The Project Plan may overlap wholly with the above Development Plan or may comprise a subset of that plan. Explain how the Project Plan contributes to, and advances, the overall Development Plan to End-of-Phase 2. If the project includes IND-enabling studies, summarize the preclinical IND-enabling plan and describe the objectives of the planned studies. Include a description of clinical operation plans. Identify potential risks to the project and describe the mitigation strategies.

Milestones: Using the Milestone template provided in Part B of the application, list the major project milestones by project year. Indicate Progress Milestones versus Go/No Go Milestones and include target completion dates and success criteria (a list of typical milestones for different development stages is provided in Sample A and an example of a completed milestone template is provided in Sample B). Milestones should describe precise, quantifiable outcomes of key activities, not simply the work to be conducted.

Timeline: Provide a timeline for the proposed project that includes key Preclinical, Clinical, CMC, Regulatory and other critical path activities, as well as major milestones.

12. IND Status *(up to 2 pages; in Part B)*
Summarize the IND status for the proposed therapeutic candidate. Summarize any pre-pre-IND discussions, pre-IND meetings and other interactions with the pertinent section(s) of the FDA regarding the proposed project. Describe any clinical hold issues and explain how they were/will be resolved. Clinical holds are expected to be resolved prior to the start of funding (Section V.A.3). If any amendments to the active IND are planned/required for the proposed project, provide evidence that studies supporting such amendments have been completed. Provide copies of any actual FDA correspondence in Part F.

13. Clinical Protocol Synopsis *(up to 8 pages in Part B Section 3)*
Using the CIRM Clinical Protocol Synopsis template, provide a synopsis for each clinical study proposed (up to 8 pages). A copy of this template has been provided as Sample D. If the proposed project starts with a clinical trial, provide the full clinical protocol in Part G (submit draft if final is not available).

14. Manufacturing Plan Synopsis *(up to 6 pages in Part B Section 4)*
Using the CIRM Manufacturing Plan Template, summarize the manufacturing strategy to support the proposed clinical studies. A copy of the template has been provided as Sample E.

15. Principal Investigator (PI), Development Team and Leadership Plan *(up to 2 pages; in Part B)*
Describe the leadership plan and organizational structure of the development team. List the key members (including consultants) and indicate their roles. Describe the plan for functional area leadership and management (including: clinical, clinical operations, regulatory, CMC, translational research). Indicate who will have responsibility for regulatory and safety filings; data collection and monitoring; and quality control. Describe the plan for oversight of CMOs/CROs. Indicate Applicant and, if applicable, Partner roles and responsibilities; describe the plan for communication, process for project

decision making, and plans for resolution of potential issues or conflicts.

16. Collaborations, Assets, Resources and Environment *(up to 3 pages; in Part B)*
Provide a list of collaborations that will participate in the proposed project (includes development partner/consultants/CROs/CMOs), or plans for identification and contracting collaborations. Summarize their specific roles, expertise and experience and explain how their participation is integral to the success of the project.

Summarize the assets, knowhow and expertise that the partner will provide (if applicable). If consultants or subcontractors will provide expertise or resources critical to the success of the project, summarize their credentials and relevant track records.

Provide a description of the facilities, environment(s), core services, and resources available for conducting the proposed project and discuss how the proposed project will benefit from unique features of these resources. Include a description of resources available for data storage and data management.

17. Clinical Sites *(up to 2 pages; in Part B)*
Provide a list of clinical sites for the proposed clinical trial. Provide evidence that the clinical sites have experience in conducting translational early Phase 1 and Phase 2 trials. Provide evidence that the clinical sites' projected patient enrollment plan is realistic.

18. Intellectual Property, Licenses and Agreements *(up to 2 pages; in Part B).*
Describe intellectual property assets (patent applications, patents), including any challenges to same and pending litigation relating to same and any licenses of rights important to development of the therapeutic. Identify any potentially blocking intellectual property known to applicant.

Provide a brief summary describing the status of Material Transfer Agreements (MTA) or licensing agreements for cell lines or other materials that are critical to the development of the therapeutic candidate and describe the role of those materials in the development of the product. In Part J, provide copies of essential MTA(s), or provide term sheets or letters of intent if an MTA has not yet been entered into. If not possible, please summarize the terms and what stage negotiations are in, including whether there is a term sheet, letter of intent, or MTA or licensing agreements.

If applicable, describe the status of letters authorizing the ability to cross reference Drug, Device or Facility Master Files (DMF, FMF). If possible provide copies of authorization letters in Part I.

19. References *(up to 2 pages; in Part B)*
List all references used in the body of the proposal.

20. Due Diligence Report **(***Part D***)**
If the proposed project has undergone a due diligence analysis by a pharmaceutical/biotechnology partner resulting in an executed development agreement, or term sheet or letter of intent to enter into a development agreement, provide a summary of the scope and extent of the due diligence investigation, including a list of specific assessments, the number and expertise of personnel involved in conducting the investigation, and a summary of key outcomes.

21. Investigator Brochure *(Part H)*
If the proposed project starts with a clinical trial, provide a copy of the Investigator Brochure for the candidate therapy. If the final is not available, submit a draft.

C. Application Submission Instructions

All applicable parts of the Strategic Partnership II Award application must be submitted to CIRM no later than 5:00 PM PDT on October 21, 2013 via the Grants Management Portal (https://grants.cirm.ca.gov). It is the applicant's responsibility to meet this deadline; no exceptions to this deadline will be made.

D. Submission of Supplemental Information

If necessary, the PI may submit limited supplemental materials that provide critical new information related to their research proposal after the application deadline but not later than 5:00 PM PST on January 6, 2014. Supplementary materials will not be accepted after this deadline. CIRM will accept a one-time-only submission of materials from the PI only if it meets the submission deadline and conforms to the requirements described herein. Accepted submissions will be forwarded to reviewers for their consideration.

The submission of supplemental materials should be in the form of a one-page letter addressed to the Associate Director of Review and submitted via email to gsambrano@cirm.ca.gov. The body of the letter may not exceed 500 words and should briefly describe the type of information submitted and when the information became available. The following materials qualify for submissions of supplemental materials:

Within the one-page letter:

- Specific citation(s) to journal publications related to the proposed project that were published or accepted for publication since the application submission deadline. You may briefly describe the significance of the publication(s) to the proposal in the cover letter.
- Confirmation of funding secured from other sources
- Regulatory (e.g., IND, IDE) filings or approvals or lifting of clinical holds occurring since the application submission deadline.
- Notice of patent application(s) filed; notice of allowance received or patent(s) issued; or notice of license(s) to relevant intellectual property (granted or received) since the application submission deadline.
- Identification of any challenges to relevant patents; updates to and pending litigation or newly initiated litigation.

The letter may not be used to describe any additional data or experiments. Changes in scope, experimental approach, or research design are not allowed.

E. Opportunity for Clarification of Submitted Information

Critical questions raised by reviewers regarding information submitted in the application will be forwarded to applicants prior to the scientific review meeting. Applicant responses will be in writing and will be made available to the GWG before the review meeting.

IX. Schedule of Deadlines and Reviews

LOI due	5:00 pm (PDT), August 22, 2013
Applications due	5:00 pm (PDT), October 21, 2013
Supplemental Information Due	5:00 pm (PST), January 6, 2014
Scientific Review of Applications by Grants Working Group (GWG)	February 5-7, 2014
Review and Approval by ICOC/Application Review Subcommittee	Q2, 2014
Earliest Funding of Awards	Q3, 2014

X. Contacts

For information about this RFA:

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For information about the review process:

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Phone: (415) 396-9103

XI. CIRM Regulations

Grant awards made through RFA 13-03A will be subject to CIRM regulations. These regulations can be found on CIRM's website at http://www.cirm.ca.gov/reg/default.asp.

A. CIRM Grants Administration Policy

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP) and the GAP for For-Profit Institutions (For-Profit GAP) serve as the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. Progress reports of research, as required by the GAP, are important to CIRM: Funding from year to year will depend on adequate scientific progress as outlined in the grant application timeline. CIRM's GAP is available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#GAP.

B. Intellectual Property Regulations

CIRM has adopted intellectual property and revenue sharing regulations for non-profit and for-profit organizations. By accepting a CIRM Grant, the Grantee agrees to comply with all such applicable regulations. It should be noted that amendments to 17 Cal. Code Regs. are currently pending with such proposed amendment available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

C. Human Stem Cell Research Regulations

As reflected in CIRM's GAP, CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010-100110 available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#standards). All research conducted under this award will be expected to comply with these standards. This information can be found on the CIRM website.

CIRM expects that clinical trials will be conducted in accordance with all applicable State and Federal regulations and in accordance with CIRM's Medical and Ethical Standards: http://www.cirm.ca.gov/files/meetings/pdf/2011/062211_Item_09_SWG_Trials.pdf.

D. California Supplier Regulation

CIRM has adopted a regulation to implement the requirement in Proposition 71 that grant and loan recipients make a good faith effort to achieve a goal of purchasing more than 50% of their goods and services from California suppliers (Title 17,California Code of Regulations, section 100502). Grant and loan recipients are required to comply with this standard.

E. Clinical Trial Registration

CIRM requires that any clinical trial funded under any of its funding programs be listed on http://clinicaltrials.gov/. CIRM will also encourage awardees to share the results, at the completion of their studies, for the benefit of the field.

F. Loan Administration Policy

In the event that the applicant chooses to receive an award in the form of a loan rather than a grant, the Loan Administration Policy (LAP) will apply and is available at: http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants and is summarized in Appendix A. Applicants should be advised that with respect to any and all RFAs, the IP and Industry Subcommittee of CIRM's board may elect to adopt terms other than the guidelines set forth in the LAP.

XII. Confidentiality of Submissions to CIRM

CIRM protects the confidential information it receives from applicants and grantees to the maximum extent permitted by law. That protection is embodied in a number of laws and policies, described below, and applies to the confidential information submitted by all applicants and grantees. CIRM does not enter into separate non-disclosure agreements with individual applicants or grantees.

A. CIRM Employees

CIRM employees are subject to the confidentiality requirements identified in a CIRM policy known as the "Incompatible Activities Statement." By law (Cal. Gov. Code § 19990) state employees are prohibited from engaging in activity identified by their employing agencies' Incompatible Activities Statements. CIRM employees are also subject to the confidentiality provision in the CIRM Employee Handbook. All employees sign statements acknowledging receipt of the Incompatible Activities Statement and the CIRM Employee Handbook.

Excerpt from Incompatible Activities Statement:

> No employee shall utilize his or her status as a CIRM employee to acquire access to confidential information other than on behalf of the CIRM.
>
> Additionally, no employee shall use such information for private gain or advantage or provide confidential information to persons to whom issuance of this information has not been authorized.

Excerpt from Employee Handbook:

> All records and information relating to CIRM and its activities are confidential and employees must, therefore, treat all matters accordingly. No CIRM or CIRM related information, including without limitation, documents, notes, files, records, oral information, computer files or similar materials (except in the ordinary course of performing duties on behalf of CIRM) may be removed from CIRM without the President's authorization. Additionally, the contents of CIRM's records or information otherwise obtained in regard to CIRM activities may not be disclosed to anyone, except where required for an official purpose or by law. Employees must not disclose any confidential information, purposefully or inadvertently through casual conversation, to any unauthorized person inside or outside CIRM. Employees who are unsure about the confidential nature of specific information must ask their supervisor for clarification. Employees will be subject to appropriate disciplinary action, up to and including dismissal, for purposefully or accidentally, revealing information of a confidential nature.

B. Clinical Development Advisory Panel

Members of CIRM's Clinical Development Advisory Panel (CDAP) sign contracts that include the following provision:

> Advisor shall keep confidential any information provided by CIRM or any information conveyed orally to Advisor by CIRM with oral notification of its confidentiality (the "Confidential Information"). Advisor agrees to maintain the secrecy of CIRM's Confidential Information and agrees not to use it except in performing the Services under this Agreement and not to disclose it to anyone outside CIRM or anyone within CIRM's organization who does not have a need to know it to perform under this Agreement. This non-disclosure provision shall not apply to any of the following:
>
> 1. Information which Advisor can demonstrate by written records was known to him or her prior to the effective date of this Agreement;
> 2. Is currently in, or in the future enters, the public domain other than through a breach of this Agreement or through other acts or omissions of Advisor; or
> 3. Is obtained lawfully from a third party.

C. Grants Working Group

The Grants Working Group (GWG) reviews grant applications. All members sign statements guaranteeing confidentiality, at the time of their appointment, and again prior to accessing application materials for each grant round.

D. Public Records Act

As a state agency, CIRM is required to allow public access to certain categories of documents held by the agency. The Public Records Act (California Government Code section 6250 et seq.) exempts certain categories of documents from public disclosure. As relevant here, agencies are not required to release trade secrets, as defined by section 3426.1(d) of the Civil Code:

> "Trade secret" means information, including a formula, pattern, compilation, program, device, method, technique, or process, that (1) Derives independent economic value, actual or potential, from not being generally known to the public or to other persons who can obtain economic value from its disclosure or use; and (2) Is the subject of efforts that are reasonable under the circumstances to maintain its secrecy.

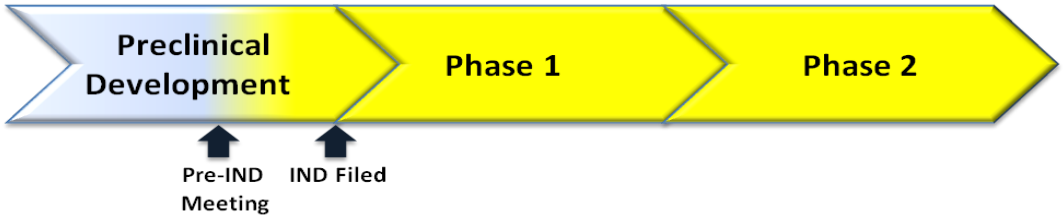
In addition, CIRM operates under special Public Records Act exemptions included in Proposition 71, the ballot initiative that created CIRM. Proposition 71 (Health & Safety Code, sec. 125290.30(e)(2)(B)-(C)) exempts from disclosure:

1. Records containing or reflecting confidential intellectual property or work product, whether patentable or not, including, but not limited to, any formula, plan, pattern, process, tool, mechanism, compound, procedure, production data, or compilation of information, which is not patented, which is known only to certain individuals who are using it to fabricate, produce, or compound an article of trade or a service having commercial value and which gives its user an opportunity to obtain a business advantage over competitors who do not know it or use it.

2. Prepublication scientific working papers or research data.

Sample A: DEVELOPMENT PROJECT MAJOR MILESTONES

The Table below lists typical major milestones for a development project going from pre-IND meeting to the end of Phase 2. Milestones are grouped by stage of development (preclinical, Phase 1 or Phase 2) and by category (CMC, pharm/tox, clinical regulatory).



	Preclinical Development	Phase 1	Phase 2
CMC	• Lock down final process • Complete Master Cell Bank • Finalize release criteria • Release GLP lot • Release GMP lot(s)	• Complete scale-up process development for future studies • Select potency assay • Manufacture GMP lots for Phase 2	• Validate potency assay
Pharm/ Tox	• Complete pivotal GLP efficacy study • Complete GLP Tox study • Complete tumorigenicity study (cell therapies only) • Complete biodistribution study • Complete delivery method safety study • Complete PK/ADME studies (sm) • Validate PK/immunogenicity assays (MAbs) • Qualify biomarker asasys	• Complete comparability studies • Demonstrate comparability of product made with original versus scale-up processes	
Clinical /Reg	• Conduct RAC review meeting (gene therapy products) • File IND Finalize Phase I protocol	• Initiate first clinical site • Enroll first patient • Complete enrollment of cohort 1 • Complete enrollment of cohort 2 • Complete enrollment of cohort 3 • Last patient in • Data base lock • Complete data analysis • Finalize Phase 2 protocol	• Initiate clinical site(s) • Enroll first patient • Complete Interim enrollment milestones • Last patient in • Data base lock

Sample B: CIRM MAJOR MILESTONES TEMPLATE

Instructions: The text below shows ***example*** milestones. To fill out the template, ***delete the example text*** and type in your own project milestones, success criteria, projected completion dates and any comments. Indicate Progress versus Go /No Go milestones. Please note: Major milestones are grouped by project year and are numbered **consecutively**.

Year 1 Milestones

	Milestone	Target completion date	Progress or Go/No Go	Comments, & Potential Risks to Timeline
CMC	1. Release GLP lot *Success criteria*: At least X million differentiated cells meeting specified release criteria	Q1 2013	Progress milestone	
	2. Release GMP lot *Success criteria*: At least X million differentiated cells meeting specified release criteria	Q4 2013	Progress	
Pharm/tox	3. Complete pivotal GLP safety study *Success criteria*: i). acceptable safety demonstrated (potential toxicities are monitorable and acceptable for target patient population); ii). Therapeutic window defined (with X safety margin between highest safe dose and target efficacious dose)	Q4 2013	Go/No Go	Assumes GLP material available by X date
	4. Complete tumorigenicity study *Success criteria*: no tumors	Q4 2013	Go /No Go	
Clinical/ Regulatory	5. File IND *Success criteria*: FDA acceptance; no clinical hold issues	Q4 2013	Go /No Go	
	6. Enroll first subject	Q1 2014	Progress	Assumes IRB approval by X date

Year 2 Milestones

	Milestone	Target completion date	Progress or Go/No Go	Comments & Potential Risks to Timeline
CMC	7. Release additional GMP lot(s) *Success criteria*: At least 2 lots meeting specified Release criteria	Q2 2014	Progress	Assumes Year 1 activities and milestones are met
Pharm/tox	8. Complete MOA study and select potency assay *Success criteria*: Assay correlates with in vivo efficacy and can detect a 30% change in potency	Q2 2014	Progress	
Clinical/ Regulatory	9. Complete enrollment of cohort 1 *Success criteria*: Enroll at least X subjects with X days of follow up 10. Complete enrollment of cohort 2 *Success criteria*: Complete enrollment of at least X patients with X days of follow up	Q2 2014 Q4 2014	Progress Progress	Assumes acceptable safety in cohort 1

Year 3 Milestones

	Milestone	Target completion date	Progress or Go/No Go	Comments & Potential Risks to Timeline
CMC	11. Complete Scale up process development	Q2 2015	Progress	
Pharm/tox				
Clinical/ Regulatory	12. Complete enrollment 13. Data base lock	Q1 2015 Q3 2015	Progress Progress	Assumes addition of X clinical sites by Q2 2014

Year 4 Milestones

	Milestone	Target completion date	Progress or Go/No Go	Comments & Potential Risks to Timeline
CMC	14. Manufacture X GMP lots for Phase 2 *Success criteria*: At least X vials passing release specs 15. Validate potency assay	Q1 2016 Q2 2016	Progress Progress	
Pharm/tox				
Clinical/ Regulatory	16. complete clinical study report			

Sample C: CIRM TARGET PRODUCT PROFILE (TPP) TEMPLATE

TARGET PRODUCT PROFILE for	
<Delete this text and type Name of your Product/Therapy here>	
INDICATION: ***Disease or condition for which your product/therapy will be indicated***	
Optimal indication and decision criteria < Delete and type your text here>	***Minimally acceptable indication and criteria*** < Delete and type your text here>
BIOLOGICAL ACTIVITY: ***Biological activity of your product/therapy***	
Optimal biological activity and decision criteria < Delete and type your text here>	***Minimally acceptable biological activity and criteria*** < Delete and type your text here>
EFFICACY: ***Proposed efficacy endpoints for your product/therapy***	
Optimal efficacy endpoints and decision criteria < Delete and type your text here>	***Minimally acceptable efficacy endpoints and criteria*** < Delete and type your text here>
SAFETY/CONTRAINDICATIONS*:* ***Potential safety risks associated with your product/therapy***	
Optimal safety profile and decision criteria <Delete and type your text here>	***Minimally acceptable safety profile and decision criteria*** <Delete and type your text here>
DOSE/REGIMEN: ***Briefly describe the proposed dose and dosing regimen of your product/therapy.***	
Optimal dose and dosing regimen and decision criteria <Delete and type your text here>	***Minimally acceptable dose and dosing regimen and decision criteria*** <Delete and type your text here>
DOSAGE FORM/ROUTE OF DELIVERY: ***Briefly describe the proposed dosage form and route of delivery for your product/therapy.***	
Optimal dosage form and route of delivery and decision criteria <Delete and type your text here>	***Minimally acceptable dosage form and route of delivery and decision criteria*** <Delete and type your text here>

Sample D: CIRM CLINICAL PROTOCOL SYNOPSIS TEMPLATE

STUDY TITLE
Provide full title of the study
CLINICAL PHASE
Specify clinical phase (1, 2a)
STUDY OBJECTIVES
Provide a brief description of the study objectives e.g., why is the study being done, what is the intent? E.g., safety, feasibility *Primary Objectives:* *Secondary Objectives:* *Exploratory Objectives:*
STUDY RATIONALE
Summarize the rationale for testing the proposed therapy
STUDY POPULATION
Briefly describe the study population and explain the rationale for choosing this population
MAIN INCLUSION/EXCLUSION CRITERIA
Specify the main inclusion/exclusion criteria and explain the rationale.
PRIMARY ENDPOINT (S)
Describe the Primary Endpoint(s) and the set of measurements used to address the objectives
SECONDARY & EXPLORATORY ENDPOINTS
Describe the Secondary & Exploratory Endpoint(s) and measures that will address them
STUDY DESIGN
Summarize the study design, including type of study, number of arms, controls or comparators
SUBJECT NUMBER
Provide the total number of study subjects, the number per study arm, and justification
TREATMENT DURATION
Specify the length of the treatment period

DURATION OF FOLLOW UP
Specify the length of the protocol-specified follow up period
DOSE LEVEL (S) AND DOSE JUSTIFICATION
Specify the dose level(s), number of doses, and dosing frequency. Summarize how dosing was determined
ROUTE OF DELIVERY
Specify how the doses will be delivered
DATA and SAFETY MONITORING PLAN (DSMP)
Summarize the Data and Safety Monitoring Plan. Describe measures that will be implemented to minimize risk to study subjects e.g. specific inclusions/exclusions; plans to ensure medical intervention in the case of an adverse event for subjects; plans for surveillance, detection and management of specific adverse events that might or could occur; potential use of an Independent Safety Monitor or Data Safety Monitoring Board (DSMB)
STOPPING RULES
Specify stopping rules
IMMUNE MONITORING & IMMUNOSUPPRESSION
Describe and justify the plan for immunosuppression and immune monitoring (if applicable)
SUPPORTING STUDIES
Summarize supporting studies that are part of this clinical study (e.g. imaging, biomarker analyses, cell phenotyping, genotyping, gene expression analyses), that will provide critical additional data to address the objectives of this RFA or inform decisions on continued clinical testing. Include: *Objectives and rationale* *Sample collections (specify type, frequency)* *Testing methodology* *Data analysis* *Special considerations*
ASSAYS/METHODOLOGIES
Briefly describe any specialized assays or methodologies that will be used in this clinical study or supporting study/studies. (Provide a more detailed summary of assay methods and summarize assay qualification/validation in Part D). Indicate where specialized testing will be conducted
STATISTICAL ANALYSIS PLAN
Summarize the Statistical Analysis Plan or describe how the data will be analyzed

OUTCOME CRITERIA
Describe criteria that would define whether you would or would not move forward with the subsequent development plan, based upon primary and designated secondary objectives
RISKS
Identify potential risks and mitigation strategies (e.g. need for and risks associated with long term immunosuppression)
CLINICAL SITES
Indicate the number of clinical sites that will participate in the study. Summarize the criteria for site selection. Provide a list of proposed sites with a brief description of the site's experience and capabilities in the conduct of clinical research.
CLINICAL OPERATIONS PLAN
Summarize the plan for managing the conduct of the clinical study. Describe plans for training clinical investigators and personnel at clinical sites and the plan for oversight and monitoring of clinical sites. Indicate who will be responsible for management and sign off of clinical operations activities.
ENROLLMENT
Describe the enrollment strategy and provide a timeline showing enrollment projections Describe plans for inclusion of women and minorities
LONG TERM FOLLOW UP
Describe requirements and plans for long term follow up and indicate how these will be supported
TIMELINE
Provide a timeline for completion of the study and indicate relevant milestones

Sample E: CIRM MANUFACTURING PLAN SYNOPSIS TEMPLATE

TEST ARTICLE
Describe the Test Article
STARTING CELL
Specify starting cell line or cellular source
MANUFACTURING PROCESS
Provide a brief description of the manufacturing process *Provide a flow diagram of the process from starting cell source to final test article* *Describe the plan for shipment of released lot from the manufacturing facility to clinical sites and describe the steps that will be performed at the clinical site*
PROCESS DURATION
Specify the duration of a manufacturing run and time required to test and release a lot
PRODUCT RELEASE
Provide a list of the product release assays and acceptance criteria
IDENTITY ASSAY
Briefly describe the Identity assay(s)
POTENCY ASSAY
Briefly describe the Potency assay(s)
ADDITIONAL CHARACTERIZATION
Briefly describe any additional characterization assays routinely performed (but not required for lot release)
LOT SIZE
Specify the average lot size (number of doses/treatments)
LOT REQUIREMENTS FOR PROPOSED CLINICAL WORK
Indicate the projected number of lots needed to support the proposed clinical work
LOT FAILURE
Specify the % failure of lot release
GMP MANUFACTURING FACILITY
Indicate where GMP manufacturing of the candidate cell therapy will be performed. Describe the experience and track record of the manufacturing facility

RELEASE TESTING FACILITY
Indicate where Release Testing will be performed. Describe the experience and track record of the testing facility
DOSE FORMULATION AT CLINICAL SITES
Briefly describe the plan for managing product quality control at clinical sites
CMC ACTIVITIES PROPOSED FOR FUNDING
Specify all CMC-related activities proposed for funding under this RFA and indicate which activities will be funded by CIRM
RISKS
Identify potential risks (e.g. potential for clinical hold, lot failures) and mitigation strategies
TIMELINE
Provide a timeline for the manufacturing runs planned to support the proposed clinical research and indicate relevant milestones
High Level Manufacturing Process Flow Diagram
Include - Material, Unit Operations and Analytical Methods (in process and release tests) and Timeline

Appendix A: LOAN INFORMATION

Loan Terms: As stated within the body of this Request for Application, a successful applicant may choose to accept the award in the form of a grant or a loan. If the award is in the form of a Loan, the CIRM and the successful applicant will enter into a loan agreement and the Loan Administration Policy (LAP) will govern. The LAP is currently being revised. The new terms, which we expect to be in effect at the time the awards are made, are summarized below. The Loan Administration Policy in effect on the date the Notice of Loan Award is issued will govern the loan.

(i) Two types of Loans, Company-Backed Loans and Product-Backed Loans, are available. Company-Backed Loans are subject to repayment regardless of the success of the project, whereas a loan forgiveness mechanism is available for Product Backed Loans. No personal guarantees or collateral are required.
(ii) Term: The term of the loan will be 5 years, subject to extensions as set forth in the LAP.
(iii) Payments: All principal and interest will be due and payable at the end of the loan term, unless the repayment obligation has been forgiven or accelerated. Loans that are extended require periodic payments of interest accrued.
(iv) Interest Rate: The interest rate for the initial term of the loan shall be LIBOR plus 2%.
(v) Warrants: Loan recipients will be required to provide CIRM with warrants; the amount of such warrant coverage will depend on the type of loan requested and satisfaction of certain criteria as outlined in the LAP.
(vi) Extension of Term: Loan Recipient may extend the initial term in one year increments (provided it is in compliance with the Notice of Loan Award and LAP), subject to (a) payment of 25% of unpaid and accrued interest and (b) an interest rate increase in the amount of 1% over the rate in effect the prior year.
(vii) Loan Administration Costs: Approved for-profit applicants who accept a loan will pay for loan administration costs out of the award. If the term of the loan is extended beyond year 5, the loan recipient must pay any additional loan administration costs.

Applicants will be informed of the actual costs once finalized.
Loan applicants will be required to submit financial information. For additional information about the loan program, consult the CIRM LAP, available at: http://www.cirm.ca.gov/reg/default.asp.