RFA 13-01: CIRM Disease Team Therapy Development III Awards

I. Purpose

The purpose of CIRM's Disease Team Therapy Development III initiative is to advance early clinical development of novel therapies derived from or targeting stem cells, potentially offering unique benefit with well-considered risk to persons with disease or serious injury. Disease Team Therapy Development III Awards will support actively managed teams to conduct milestone-driven preclinical and clinical development.

II. Objectives and Scope

The objective of a Disease Team Therapy Development III award will be to achieve, in 4 years or less, the completion of an early clinical trial under an Investigational New Drug (IND) application filed with the Food and Drug Administration (FDA).

Proposed projects must complete one or more of the following:

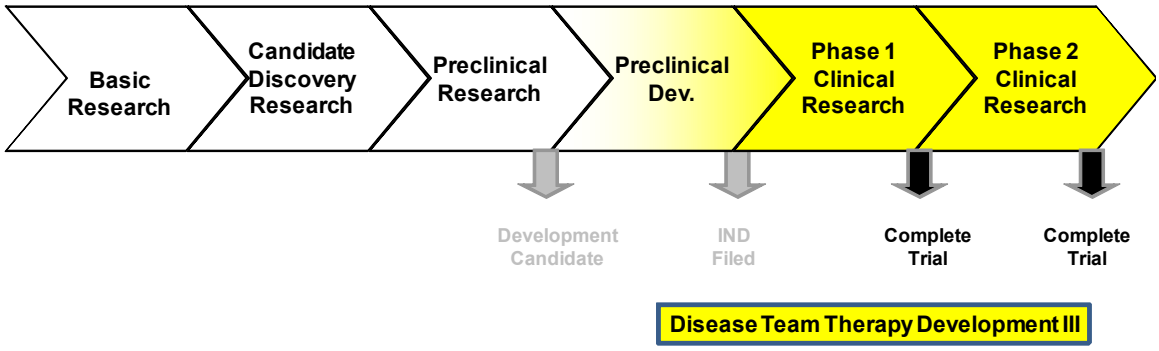
- A Phase 1 clinical study to demonstrate preliminary safety, assess measures of biological/clinical activity in humans, and determine a range of safe doses to be studied in subsequent trials.
- A Phase 2 clinical study to evaluate both safety and efficacy of the candidate therapeutic.
- For CIRM-funded Early Translational awardees only, file a complete and well-supported IND.

CIRM will only fund programs that include a clinical study that can be completed and analyzed within the four-year project period. In this RFA, 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 a limited amount of IND-enabling as well as clinical research.

In addition to the objective of completing an early phase clinical trial, in order to

ensure access to a development path for prior CIRM-funded projects, this RFA includes an Early Translational Allowance Pathway which requires filing a complete and well-supported IND with the FDA within the award period. An Early Translational Allowance is available only to CIRM Early Translational awardees who have been determined to be eligible to apply by CIRM. Please see Section V.G for further information.

The scope of the Disease Team Therapy Development III Awards is illustrated in the figure below.



The key objective of the Disease Team Therapy Development III RFA is to complete a clinical trial. This Award will support activities 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 Phase 1 clinical study proposed as part of the project.
- Supporting activities to enable the proposed clinical study such as GMP production for the proposed trial(s) 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.

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

examples:

- Early research and translation activities leading up to selection of a therapeutic development candidate
- cGMP production for Phase 3 studies.
- Phase 3 clinical studies
- 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 for the funded project

Priority will be given to eligible proposals that meet one of the following:

- Proposals that include a Phase 1 or Phase 2 clinical study that could demonstrate clinical proof-of-concept if successful.
- Proposals aimed at furthering the development of successfully completed CIRM-funded projects.
- Proposals that cannot, or are unlikely to, receive timely or sufficient federal funding.

The scope and priority areas identified within this RFA will be used to invite full applications based on the LOIs that will yield the best possible research proposals.

III. Award Information

A. Award

Under this RFA, CIRM expects to commit up to $100 million to support up to 5 awards. CIRM will fund between $5 million and $20 million of the total costs of a proposed project over four years or less (justifiable costs include direct project costs, direct facilities costs, and indirect costs). Only in extraordinary cases is it expected that a project would be funded at the higher end of the range.

B. Co-Funding

Since small molecules and biologics have more of a track record with industry and with the FDA, CIRM is targeting these therapeutic classes for required co-funding while allowing more latitude for stem cell based therapies. CIRM will

require co-funding from applicants proposing to conduct a clinical trial(s) using a small molecule drug or biologic. Costs requiring co-funding include costs associated with conducting the clinical trial as well as manufacturing the therapeutic under the IND. Applicants proposing a clinical trial with a small molecule or biologic must match 25% of the CIRM funding requested for the clinical trial direct costs as calculated in the Activity Based Budget workshop (see Part D for co-funding calculation). Co-funding may come from the applicant's own assets, from an industry partner, or from another funding source arranged by the applicant. Co-funding can be in the form of matching funds and/or in-kind services.

C. Award Mechanism

CIRM expects to fund approved proposals through grants or loans. Awards to non-profit organizations will be in the form of a grant. For-profit organizations may choose to accept the award in the form of a grant or a loan. Sponsorship of the IND will define the applicant organization (see Section V).

Grant Terms: Grants are funded through quarterly or semi-annual disbursements (at CIRM's option) and are subject to CIRM's intellectual property regulations, including the revenue-sharing provisions in 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. § 100608(b) is currently pending. The proposed amendment is available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

Loan Terms: The terms of the Loans are set forth in detail in Appendix A of this RFA. Loan recipients shall be governed by the CIRM Loan Administration Policy that is in effect as of the date of the execution of the Notice of Loan Award. 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. For information on the loan program, consult the CIRM Loan Administration Policy, available at: http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

D. Award Administration

Given the urgency of CIRM's mission, all approved applications must be initiated (award start date in issued and signed Notice of Grant or Notice of Loan Award) within 6 months of approval and authorization for funding by 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 or Early Translational award, funding cannot be used for activities funded by the already existing award. In the case of awards to applicants for continuation of a prior CIRM-funded project, any funding disbursed to the applicant under this RFA will not commence until the prior award is closed.

For all awards, CIRM reserves the right to negotiate funded project activities, milestones, success criteria, timelines and budgets prior to issuance of the Notice of Grant Award (NGA) or Notice of Loan Award (NLA). Progress in translational research is important to CIRM. Continued funding is contingent upon timely scientific progress as outlined in the project milestones and timeline established under the NGA or NLA. If milestones are not met, CIRM reserves the right to terminate the project or to negotiate new milestones to refocus/redirect the project.

In addition to providing annual Progress Reports, as required by the Grants Administration Policy ("GAP"), (see Section XII.A of this program announcement), grant and loan recipients are required to: 1) respond to information requests by CIRM; 2) provide quarterly progress updates to CIRM; 3) notify CIRM of any serious adverse event related to the therapeutic candidate in a clinical trial, as required by the GAP (see Section XII.A of this RFA); 4) meet with CIRM's Clinical Development Advisory Panel (CDAP) approximately once each 12-month period and at key decision points; 5) submit regulatory documentation such as pre-IND Briefing package, formal minutes from agency meetings and other agency correspondence to CIRM and 6) notify CIRM in advance about upcoming regulatory meetings and permit CIRM staff to attend such meetings.

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

IV. Collaborative Funding Partners

CIRM has established a program with other agencies that fund stem cell and regenerative medicine research. Through this Collaborative Funding Partner (CFP) program, California-based Principal Investigators (PIs) can collaborate with a Funding Partner PI ("Partner PI") from a Funding Partner applicant institution ("partner applicant institution") eligible for funding from one of CIRM's CFPs to bring important additional resources to the project. If a collaboratively funded proposal is approved (a "CIRM/CFP Award") CIRM will fund all project

research conducted within the State of California and the CFP will fund all project research conducted within its jurisdiction. For this RFA, the Medical Research Council (MRC) of the United Kingdom, the Chinese Ministry of Science and Technology (MOST), the National Institutes of Health (NIH), and the Andalusian Initiative for Advanced Therapies (Initiativa Andaluza en Terapias Avanzadas, "IATA") of Andalusia, Spain will participate as CFPs.

To apply for a collaboratively funded project involving CIRM and a CFP, applicants must satisfy both the CIRM requirements (Section V) and any additional requirements established by the CFP. For more details on these requirements please see Appendix B, C, D, or E.

Before funding contracts are signed, successful CIRM/CFP applicant teams must have a signed written agreement adequately addressing Intellectual Property (IP) issues relating to the collaborative project and must provide copies to CIRM and the CFP. These IP Agreements will be reviewed by both CIRM and the CFP to ensure that they are consistent with the applicable regulations of CIRM and the CFP and with the Agreement between the co-funders.

Before funding contracts are signed, successful CIRM/CFP applicant teams must obtain all necessary approvals for animal protection, human subject protection, and use of human embryonic stem cells, unless the approval is not required to initiate the award. CIRM and the CFP will monitor compliance with approval procedures required in their respective jurisdictions.

Both CIRM and the CFP may be involved in the management/oversight of the CIRM/CFP award, by participating in mutually agreed upon joint award administration activities. These activities may include but are not limited to participation in progress monitoring via progress reports and discussion with a Clinical Development Advisory Panel (CDAP).

Disclosure Information

All applicants, including those not applying with a Partner PI are hereby notified that CIRM may share Disease Team Therapy Development III Award application and related information submitted by applicants with the CFP in order to facilitate their participation in the RFA. Information concerning approved CIRM/CFP Awards may also be shared with the CFP. Before receiving any such material, the CFP will agree in writing to hold the materials in strict confidence and to use them solely for purposes directly related to this RFA.

V. Eligibility

For an **investigator-sponsored IND**, the investigator-sponsor must be the Principal Investigator (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 that organization.

Applicants with projects beginning with IND-enabling studies must, by the Letter of Intent (LOI) due date (March 13, 2013), either have completed a 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 (May 15, 2013).

Applicants with projects beginning with a clinical trial must have filed a complete IND application package with the FDA by the LOI due date (March 13, 2013). Applicants with an MRC Partner PI should refer to Appendix B for information regarding UK-based clinical trials.

CIRM requires that any proposed clinical trial must include at least one clinical trial site in California. CIRM expects its 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 inclusion is inappropriate with respect to health of the subjects or the purpose of the research.

A. Project Eligibility

The following project eligibility criteria apply to all applicants, with the exception of projects that are a continuation of prior CIRM-funded Early Translational award. See Section V.G., below.

i. 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 IND application filed with the FDA. The proposed clinical trial(s) will evaluate preliminary safety and assess measures of preliminary biological activity/efficacy in humans.

ii. Therapeutic Candidate

Each funded Research Award will support a project for a single therapeutic candidate that is or will be the subject of a single IND filing with FDA and meets any of the following criteria:

- A cell therapy derived from pluripotent stem cells
- Allogeneic adult stem cells or progenitor cells for repair and/or regeneration, except for those out of scope identified below
- Genetically- or pharmacologically-modified hematopoietic stem cells
- ~~Genetically- or pharmacologically-modified allogeneic adult stem cells or progenitor cells (e.g. hematopoietic stem cells) for repair and/or regeneration~~

- Tissue engineered (e.g utilizing a cell scaffold or biomaterial in combination with a stem or progenitor cell) functional tissues for implantation in vivo
- A small molecule or biologic demonstrated to target normal endogenous stem cells as the primary mechanism of action (MOA) (in vivo) for regeneration and repair
- Any therapeutic candidate developed under a Disease Team Research I (RFA 09-01) award

A project that proposes a therapeutic candidate that is substantially comparable to one already represented in CIRM's translational portfolio (see Appendix E) should provide a compelling justification for doing so.

Therapeutic candidates that fall outside the scope of this RFA include the following:

- Unmodified hematopoietic stem cells (HSCs)
- Small molecules and biologics, unless targeting endogenous stem cells as primary MOA (in vivo) for regeneration or repair
- Autologous mesenchymal stem cell (MSC) approaches
- Autologous tissue-derived stem cell-derived approaches
- Minimally manipulated bone marrow or minimally manipulated cord blood

iii. Readiness

Disease Team Therapy Development III Awards is designed to capture mature development projects that are at or near the stage of early clinical research. Eligible projects 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 has been shown with the development 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 (March 13, 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 (May 15, 2013). Based on the outcome of that discussion, the project should be projected to be within 12-18 months of IND filing.
- For projects starting with a Phase 1 clinical trial, the applicant must have filed an IND package with the FDA by the LOI deadline (March 13, 2013). Any clinical hold issues not resolved by the full application deadline (May 15, 2013) should be projected to be resolved by the time of funding.

- For projects proposing 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 (May 15, 2013).

B. Institutional Eligibility

Both non-profit and for-profit organizations may apply. At the time of the Research Award application deadline, the applicant organization must be located in California (that is, the organization must have employees who are conducting business or operations at a location in California). At the time of funding, the applicant organization must be conducting or managing research that is taking place in California. If these requirements are not met, CIRM may terminate all further action on the application.

“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. For-profit applicant organizations that hold 2 or more of the following active awards as of the application due date, May 15, 2013 are not eligible to apply for this award: Disease Team, Disease Team Therapy Development, and/or Strategic Partnership.

C. Principal Investigator (PI) Eligibility

CIRM requires that a single Principal Investigator (PI) and a single applicant organization (the PI’s organization) be designated in each 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.

A PI may submit only one application under this RFA. 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 in the California office of the applicant organization and have demonstrated expertise 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, an investigator may participate as a PI or a Co-PI on only one active CIRM Disease Team, Disease Team Therapy Development, or Strategic Partnership award as of the funding start date for a Disease Team Therapy Development III award.

Investigators who are already a PI or a Co-PI on an active CIRM Disease Team, Disease Team Therapy Development or Strategic Partnership award must complete or relinquish their existing award prior to start of funding for a Disease Team Therapy Development III award.

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. This RFA is not open to investigators who are already a PI or Co-PI on 3 or more active or awarded CIRM awards as of May 15, 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.

D. Co-Principal Investigator(s) Eligibility

In order to ensure adequate expertise and experience on the project leadership team, CIRM will allow for a single CIRM-funded Co-Principal Investigator (Co-PI). The Co-PI must have an M.D., Ph.D. or equivalent degree and must be sponsored by the institution at which the Co-PI will conduct the proposed project. By the full application deadline (May 15, 2013), the Co-PI must:

- Be an independent investigator in California at the sponsoring non-profit institution, or have an equivalent position and be an employee in California (at least 50-percent time) of the for-profit institution;

- Have documented authority from the sponsoring institution to staff the proposed project; and

- Have documented commitment from the sponsoring institution to provide appropriate space and resources sufficient to carry out the proposed research.

Designating a Co-PI is not a requirement of this award. The decision of whether to include a Co-PI should be guided by the goals of the project. The Co-PI role is not intended to substitute for any of the responsibilities or effort contributions of the PI. The Co-PI role is most appropriate for leading a substantive and critical portion of the proposed project that is supported by a dedicated budget. All applications will require a leadership plan. When considering a Co-PI, please be aware that the reviewers will consider the structure and governance of the development team as well as the knowledge, skills and experience of the individual PI and Co-PI. The Co-PI is responsible and accountable to the grantee organization.

E. Project Manager Eligibility

CIRM requires a project management professional (Project Manager) be designated in each 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.

F. Extraordinary Exceptions

In extraordinary circumstances, the President has the discretion to permit exceptions to requirements or limitations in Section V of this RFA. 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 further the objectives of this RFA and must comply with the requirements of Proposition 71 and all applicable California state regulations, including the Grants Administration Policy (see Section XII of this RFA) and the Loan Administration Policy (see Appendix A of this RFA), or they will not be considered.

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 XI.

G. Early Translational Allowance Pathway Eligibility

In order to facilitate successful translational projects access to a pathway to clinical trials, a limited number of CIRM Early Translational awards may be considered for awards under this RFA. For the purpose of eligibility for this RFA, a successful project is defined by CIRM as having met by the application submission date or having a high likelihood of meeting by the end of 2013 prior to funding all of the below activities (Section V.G.iii) and all milestones in the Early Translational award NGA. Otherwise, CIRM may discontinue the application.

Applicants with Early Translational awards seeking to utilize this exception pathway will differ in Eligibility (see this section below) and Review Criteria (see Section VIII) in several key ways.

i. Project Objective for Early Translational Allowance Pathway.
The proposed project must address a serious unmet medical need/injury and must file a complete and well-supported IND with the FDA (and, if desired, other regulatory agencies) within the award period. A copy of the IND package with the included clinical protocol and an investigator brochure will be provided to CIRM. In addition, CIRM will require a development plan through the End-of-Phase-2 by the completion of the award.

ii. Therapeutic Candidates for Early Translational Allowance Pathway.
Each funded award will support a project for a single therapeutic candidate that will be the subject of a single IND filing with the FDA. Therapeutic candidates developed under Early Translational RFAs 08-05 and 10-01 are eligible to apply; however, any small molecule or biologic must target an endogenous stem cell or a cancer stem cell.

iii. Readiness for Early Translational Allowance Pathway.
In order to be considered eligible for this RFA, a project funded by a CIRM Early Translational Award (RFA 08-05 or RFA 10-01) must meet or have a high likelihood of meeting the following criteria. Where noted criteria must be met by the application submission date (May 15, 2013); otherwise criteria must be met by the end of 2013, prior to funding if awarded. If these criteria are not met, CIRM may discontinue the application.

- By the application submission date (May 15, 2013) a single final therapeutic development candidate has been chosen as part of the Early Translation award, in accordance with agreed to criteria, for which there is strong scientific and clinical rationale for the intended clinical use. The selected development candidate is the intended therapeutic candidate that is the subject of this application.

- Strong preclinical proof-of-concept (preferably in model for the target disease) has been shown with the development candidate (by the application submission date).
- Compelling, reproducible evidence for disease modifying activity has been shown with the development candidate in a relevant animal model(s) of the target disease/injury.
- Preliminary assessments of dose and safety (including overt toxicity, immunogenicity and/or genomic integrity, if applicable) with the therapeutic candidate have been performed and suggest an adequate therapeutic window and acceptable safety
- Studies on potential mechanism(s) of action have been conducted with the candidate and provide a reasonable scientific rationale for the proposed therapeutic approach to the target disease/injury.
- Assays are in place for characterization (identity, purity and activity) of the intended candidate (by the application submission date).
- Methods have been developed for reproducible production of the purified candidate for research and preclinical studies (by the application submission date).
- Early Translational Award NGA milestones have been met.

VI. Application and Evaluation Process

Submission of an application for a Disease Team Therapy Development III Award involves a two-step process. An eligible applicant (see Section V for eligibility criteria) must first submit a Letter of Intent (LOI). 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. Applicants will be notified if their LOI is NOT accepted.

Applications for the CIRM Disease Team Therapy Development 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.

CIRM's priorities for this RFA include:

- Proposals that include a Phase 1 or Phase 2 clinical study that could demonstrate clinical proof-of-concept if successful.
- Proposals aimed at furthering the development of successfully completed CIRM-funded projects.
- Proposals that cannot, or are unlikely to, receive timely or sufficient federal funding.

If the project proposes a therapeutic candidate that is substantially comparable to one already represented in CIRM's translational portfolio (see Appendix E) the project must be compelling.

The GWG will make funding recommendations to CIRM's governing board, the ICOC, which will make final funding decisions.

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. (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 XIII.

VII. Review Criteria

Applications will be evaluated for scientific merit by the GWG in eight key areas: 1) Significance and Impact; 2) Scientific Rationale and Risk/Benefit; 3) Therapeutic Development Readiness; 4) Design and Feasibility of the Project Plan; 5) Principal Investigator, Development Team and Leadership Plan; 6) Budget; 7) Quality of Collaborations, Assets, Resources and Environment; and 8) Intellectual Property. The specific criteria for review of applications are based on the standard review criteria described in the CIRM Grants Administration Policy (GAP, see Section XII of this RFA). Applications submitted through the Early Translational Allowance Pathway have different criteria for 3) Therapeutic Development Readiness; 4) Design and Feasibility of the Project Plan. See Section VIII.

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

1. Significance and Impact

a. 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.

b. Clinical Competitiveness and Impact: Evaluate whether the proposed therapeutic candidate could have a significant impact on standard-of-care management of the target disease/injury and if it would offer 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.

c. Responsiveness**:** Evaluate whether the proposed activities could potentially achieve one or more of the objectives of this RFA.

2. Scientific Rationale and Risk/Benefit

Assess whether 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 intended therapeutic candidate will have clinical benefit for patients and is the potential risk to subjects manageable and acceptable in the context of the target patient population?

3. Therapeutic Development Readiness

Assess whether sufficient data have been shown using the intended therapeutic candidate to provide reasonable expectation that the stated project objective(s) (e.g. IND filing and early phase clinical trial and/or early phase clinical trial) are achievable within the award period. If applicable, preclinical proof of concept data provided should be in a relevant disease or injury model and using the intended clinical product.

4. Design and Feasibility

Assess the following**:**

a. Development Plan to End-of-Phase 2: (End-of-Phase 2 is here defined as completion of early clinical studies providing sufficient information on safety, efficacy and dose, 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.)

Evaluate whether the overall Development Plan to End-of-Phase 2 is well thought out and achievable. Determine if this Development Plan supports achievement of the Target Product Profile.

b. 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:

- The proposed project is integral to the Development Plan to End-of-Phase 2.
- The overall Project Plan is feasible and could meet the objective of this RFA, which is to complete a clinical trial within the project period.
- The project milestones capture key activities and are reliable indicators

of the project's progress.
- The criteria for Go/No Go decisions are adequately defined.
- The project timeline is realistic and achievable.

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

i. 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? Are major issues raised during the pre-IND meeting being addressed?
- Is the preclinical plan sufficiently well considered and complete to enable regulatory approval to advance to a clinical trial and to potentially enable follow-on funding?
- Based on the outcome of the pre-IND meeting with FDA, is it feasible to expect filing of a well-supported and approvable IND within 12-18 months of the funding start date?

ii. Feasibility of the *regulatory path*:
- 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 in October 2013)?

iii. Feasibility of the *manufacturing strategy*:
- Assess the feasibility of the manufacturing strategy to supply the proposed clinical trial and to support scale up for future larger trials and commercialization.

iv. Design and Feasibility of the proposed *Clinical Study*:
- The proposed study is well-designed and could achieve the RFA objectives of evaluating both preliminary safety and assessing measures of biological activity/ efficacy in humans. The trial is designed to meaningfully test or elucidate mechanism(s) of action of the therapeutic such that, regardless of clinical outcome, information will be gained.
- The choice of patient population is appropriate.
- Enrollment projections are realistic and the study can be completed during the award period.

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

Assess the following:

a. Expertise and Track Record of PI: Assess whether the PI has relevant experience in therapy development, has demonstrated successful leadership experience, and will have a key role in the proposed project.

b. Development Team and Leadership Plan: Evaluate whether an appropriate

multidisciplinary team has 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?

Assess whether the PI has developed a leadership and communication plan that will ensure successful execution of the project. This plan includes progress monitoring, project decision-making and conflict resolution.

c. Clinical Investigators and Clinical Sites: Evaluate if the lead clinical investigators have relevant experience in the target disease area and in conducting clinical studies. Assess whether the clinical sites have staff experienced in conducting phase 1 and phase 2 trials.

6. Budget

Assess if the proposed budget, both overall and for key activities, is appropriate and well justified. Projected costs for key activities (such as IND-enabling activities (if any), CMC activities, clinical trials) are shown and are adequately detailed. Only in extraordinary cases is it expected that a project will be funded at the higher end of the award size range ($5 million to $20 million). Extraordinary cases might include a cell-based therapeutic with high manufacturing costs or high clinical trial costs. Any budget issues identified may; however, result in reduction or removal of budget items at the time of award.

7. Collaborations, Assets, Resources and Environment

Assess the following:

a. Collaborations: Determine whether collaborations needed for the success of the project are in place. If applicable, partnership with industry has been established to accelerate the development program, for example by contributing expertise, technology, and/or assets.

b. Clinical Trials: If the applicant is proposing to conduct a clinical trial using a small molecule or biologic, assess whether they have secured the required co-funding equivalent to 25% of the costs of the clinical trial. Although not required, consideration will be paid to applicants proposing to conduct a clinical trial using a cell therapy product and have secured co-funding for the proposed trial.

c. Contract Services: Assess whether the proposed CROs/CMOs/consultants have the experience and expertise to successfully meet expectations, deliverables and timelines and if the development team has appropriate oversight expertise.

d. Resources and Environment: Comment on whether the necessary facilities, major equipment, and services are available for conducting the proposed research. The applicant institution (including Co-PI, sponsoring institution(s), and/or Partner PI applicant institution, if applicable) is committed to supporting translational research and early phase clinical trials.

8. Intellectual Property and Licenses

Evaluate whether relevant assets (i.e. intellectual property (IP) and/or licenses) are available to the project. Has the applicant demonstrated that any critical IP, Material Transfer Agreements (MTAs) or license agreements necessary to enable development of the therapeutic candidate, are 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 IX.B, Part I)? Do the applicants have agreements in place to cross-reference Drug, Device or Facility Master File(s) (see Section IX.B, Part H) with the appropriate regulatory agency?

VIII. Review Criteria - Early Translation Allowance Pathway

Review criteria for applications utilizing the Early Translational Allowance pathway will be similar to all other applications. Because Early Translational Allowance applications will be at an earlier stage of development and are not expected to complete a clinical trial within the award period, key differences and unique review criteria are addressed below.

These review criteria apply only to Early Translational Allowance Pathway Applications. If not otherwise addressed in the section below, the Review Criteria for all applicants (Section VII) apply to Early Translational Allowance Pathway Applications. The Review Criteria outlined below correspond to and replace those defined in Section VII only for Early Translational Allowance Pathway applicants.

3. Early Translational Allowance - Therapeutic Development Readiness

For those projects eligible through the Early Translational allowance pathway, sufficient data has been shown using the intended therapeutic candidate to justify entry (and investment) into IND-enabling development. There is existing preliminary data or the project is on track to demonstrate all of the following by the end of 2013:

- Assays are in place for characterization (identity, purity and activity) of the intended candidate (by the application submission date).
- Methods have been developed for reproducible production of the purified

candidate for research and preclinical studies (by the application submission date).

- There is compelling, reproducible evidence for disease modifying activity in relevant animal model(s) of the target disease/injury with the therapeutic candidate.
- The evidence for mechanism of action, including studies with the therapeutic candidate, provides a reasonable scientific rationale for the proposed therapeutic approach to the target disease/injury.
- Preliminary studies of dose and safety (including overt toxicity, immunogenicity and/or genomic integrity, if applicable) with the therapeutic candidate have been performed and suggest an adequate therapeutic window and acceptable safety.
- Studies have been conducted with the therapeutic candidate to address the route of administration and method of delivery.

4. Early Translational Allowance - Design and Feasibility

a: Development Plan to End-of-Phase 2. Not applicable for these applications, as this will be a key deliverable for any Early Translational applicants who are successfully awarded a Disease Team Therapy Development III Award.

b: Project plan. The Project Plan describes the scope of work that will be conducted during the award period.

Evaluate the design and feasibility of the Project Plan with respect to the following:

- The overall Project Plan is feasible and could meet the objective of filing a complete and well-supported IND with the FDA within the project period.
- The project milestones capture key activities and are reliable indicators of the project's progress.
- The criteria for Go/No Go decisions are adequately defined.
- The project timeline is realistic and achievable.

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

i. Feasibility of the *preclinical plan*:
   - Is the preclinical plan sufficiently well considered and complete to enable regulatory approval to advance to a clinical trial and potentially to enable follow-on funding? If a pre-pre-IND and/or pre-IND meeting has already been held, are major issues raised during the meeting(s) being addressed?
   - Is it feasible to expect filing of a complete and well-supported IND within the project period?

ii. Feasibility of the *regulatory path*:
   - Assess whether regulatory interactions appropriate for the stage of

product development have been conducted or planned and that the regulatory path for the Development Candidate is feasible.

iii. Feasibility of *the process development and manufacturing strategy*:
- Assess the feasibility of the process development (including assay development) and manufacturing plans to achieve an appropriately scaled process and supply IND enabling activities and the first in human clinical trial (if applicable).

iv. Design and Feasibility of the proposed *Clinical Study*:
- Not applicable for Early Translational Allowance Pathway applicants.

5. Early Translational Allowance - Principal Investigator (PI), Development Team and Leadership Plan

b: Development Team and Leadership Plan. Note that a Clinical Lead is not required for Early Translational Allowance Pathway applications.

c: Clinical investigators and Clinical Sites. This category is not applicable to Early Translational Allowance Pathway applications.

IX. Application Procedure

Applicants must follow these instructions for submission of a Letter of Intent and a Disease Team Therapy Development III Award application. Applications will only be accepted from PIs who submitted a Letter of Intent that was accepted by CIRM. Applicants will be notified if their LOI was NOT accepted. 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)

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 RFA, which is to complete a clinical trial (or for Early Translation Allowance Pathway to file a complete and well-supported IND). See below and refer to the LOI instructions and form.

Early Translational Allowance Pathway applicants will be required to upload with their LOI a progress update document addressing: 1) current status toward completion of the project milestones and 2) demonstration of eligibility as defined by the criteria listed in Section V.G.

The completed LOI 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 5:00PM (PDT) on March 13, 2013. No exceptions will be

made.

B. Application Forms
Application forms for this RFA will be available via the Grants Management Portal at https://grants.cirm.ca.gov in January 2013.

The application for this PA consists of up to **nine parts**:

Application Part	Description	General Applicants	ET Allowance Path Applicants
A	Application Information Form	Required	Required
B	Proposal	Required	Required
C	Biographical Sketches	Required	Required
D	Activity Based Budget	Required	Required
E	Regulatory Correspondence	Required	Required, if any
F	Clinical Protocol	Required	Not applicable*
G	Investigator Brochure	Required	Not applicable*
H	Authorization for cross reference	Required, if applicable	Required, if applicable
I	Licenses and agreements	Required	Required

*These items will be required as deliverables to CIRM by the end of the award period.

Part A: Application Information Form (Web-based form) Part A includes: Abstract, Public Abstract, Statement of Benefit to California, Key Personnel, Budget, Budget Justification and Related Business Entities Disclosure (section numbers 1- 6 below).

Part B: Disease Team Therapy Development III Proposal (MS Word template) Part B 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 (section numbers 6-18 below).

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

Part D: Activity Based Budget

Part E: Regulatory correspondence. Copies of regulatory correspondence with the FDA must be provided. If the project includes an MRC Partner PI and

there has been regulatory interaction with the Medical and Healthcare Products Regulatory Agency (MHRA) please also provide information associated with those discussions.

Part F: Clinical Protocol. Required for projects proposing starting with a clinical trial. If final is not available submit draft.

Part G: Investigator Brochure. Required for projects proposing starting with a clinical trial. If final is not available submit draft.

Part H: Copies of authorization for cross reference of Drug, Device or Facility master files.

Part I: 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)*

P1. Project Description: Briefly describe the proposed therapeutic candidate and summarize the scientific rationale for the proposed intervention in the target disease/injury.

P2. 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

P3. Proposal Overview: Summarize the proposed project plan and describe how it will achieve: (a) the overall objectives of the Disease Team Therapy Development III Program, which is to bring therapies through development and (b) the specific objective of this RFA, which is to complete a clinical study within the 4-year project period or (only for Early Translational Allowance Pathway applications) to file a complete and well supported IND application with the FDA.

P4. Milestones: Summarize high level milestones to be achieved within the four-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. Therefore, do not include proprietary or confidential information, or information that could identify the applicant and

applicant organization.

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 the applicant (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 (if not at the applicant organization) 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 need not be listed. 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, the Co-PI (if any), who is required to commit a minimum of twenty percent (20%) 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 with, in particular, team leadership, conduct of clinical studies and/or contributions 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 Product Development Lead, CMC Lead, Preclinical Lead, Regulatory Lead and Clinical Lead) and for the lead clinical investigator at each proposed site (not applicable for Early Translational Allowance Pathway applicants). Thereafter, include all remaining biosketches in alphabetical order.

5. Budget *(included in Parts A and D)*
Provide all budget information requested in the budget section of Part A and in Part D. Specify and provide well-justified budgets for subcontracts and consultants in the appropriate section in Part A. In the activities-based budget spreadsheet (Part D), 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. The budget should clearly differentiate costs (if any) for preclinical and/or IND-enabling studies from those for executing the proposed clinical trial. Only in extraordinary cases is it expected that a project will be funded at the higher end of the range of the possible award size (see Section III.A). All allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see Section XII.A of this RFA). Guidance will be provided separately by the MRC of the United Kingdom (See Appendix B), MOST of China (see Appendix C), the NIH (see Appendix D), and IATA of Andalusia (see Appendix E).

Under this RFA, CIRM-funded allowable costs include the following:

- ***Salaries for Key Personnel and other Support Staff***
  Salaries for personnel may include the Principal Investigator 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 Disease Team Therapy Development 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 GAP (see Section XII.A of this RFA).

- ***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 (17 Cal. Code Regs., § 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, GMP production*. (Clinical trial execution would include blinding, randomization, patient recruitment, patient treatment, medical monitoring, data collection, clinical site selection/site initiation and 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 percent for for-profit applicants, and to 20 percent for non-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 Co-Investigator, consultant or subcontractor. If the application does not seek funding for any such for-profit organizations, indicate that on 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 in this RFA)*

Provide a target product profile (TPP) for the proposed therapeutic candidate. The TPP provides the aspirational product attributes 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 Target Product Profile template in Part B of the application (see Sample B 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 CDER-regulated products.

8. Clinical Competitiveness and Impact *(up to 1 page 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 demonstrating proof of concept using 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.

In addition for Early Translational Allowance Pathway applicants only, use this section to also address therapeutic development readiness (see Section VIII.3).

10. Development Plan to End-of-Phase 2 *(up to 3 pages in Part B; not applicable to Early Translational Allowance Pathway applicants)*
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.4), 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. 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 of this RFA 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 (preferably in Gantt format) 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 regulatory agency 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.iii). 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 E.

13. Clinical Protocol Synopsis *(up to 8 pages in Part B Section 7)*
Using the CIRM CLINICAL PROTOCOL SYNOPSIS template, provide a Clinical Protocol Synopsis for each clinical study proposed (up to 8 pages). A copy of this template has been provided as Sample D of this RFA. 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 for *(up to 6 pages in Part B Section 8)*

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 of this RFA. Early Translational Allowance Pathway applicants use the template to describe current process, assays and process development and manufacturing plans.

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 which team members 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 (includes development partner)/consultants/CROs/CMOs (or plans for identification and contracting) that will participate in the proposed project. Summarize their specific roles, expertise and experience and explain how they are integral to the success of the project.

If applicable, summarize the assets, knowhow and expertise that the partner PI will provide. 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 brief 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, not applicable to Early Translational Allowance Pathway applicants)*
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 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 and pending litigation relating to same and any licenses or rights important to development of the therapeutic. Identify any intellectual property known to applicant that may restrict the applicant's freedom to operate.

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 I, provide copies of essential MTA(s). If no MTAs or licensing agreements have been executed, provide term sheets or letters of intent. If that is not possible, summarize your progress to date in obtaining MTAs or licensing agreements.

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

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

20. Investigator Brochure *(Part G)*
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.

B. Application Submission Instructions

All applicable parts of the Disease Team Therapy Development III Award application must be submitted to CIRM no later than 5:00 PM PDT on May 15, 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.

C. 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 PDT on July 15, 2013. 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 should be in the form of a one-page letter addressed to the

Associate Director, 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 after 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 imposing 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.

D. 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.

X. Schedule of Deadlines and Reviews

LOIs due	5:00 pm (PDT), March 13, 2013
Applications due	5:00 pm (PDT), May 15, 2013
Scientific Review of Applications by Grants Working Group (GWG)	August 2013
Review and Approval by ICOC	Q4 2013
Earliest Funding of Awards	Q1 2014

XI. Contacts

For information about this RFA:

Kevin Whittlesey, Ph.D.
Science Officer

California Institute for Regenerative Medicine
Email: kwhittlesey@cirm.ca.gov
Phone: (415) 396-9311

For information about the review process:

Gilberto R. Sambrano, Ph.D.
Associate Director, Review
California Institute for Regenerative Medicine
Email: gsambrano@cirm.ca.gov
Phone: (415) 396-9103

XII. CIRM Regulations

Grant awards made through this RFA 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) and the Loan Agreement Policy (LAP) establish the standard terms and conditions of grant and loan 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 and the notice of grant/loan award. CIRM's GAP and LAP are 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.

C. Human Stem Cell Research Regulations

As reflected in CIRM's GAP, CIRM has adopted medical and ethical standards for human stem cell research (17 Cal. Code Regs., §§ 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 (see 17 Cal. Code Regs., 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.

XIII. 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.

CIRM Employees

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 activities 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.

Clinical Development Advisory Panel

Members of CIRM's Clinical Development Advisory Panel 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.

Grants Working Group

The Grants Working Group 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.

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.

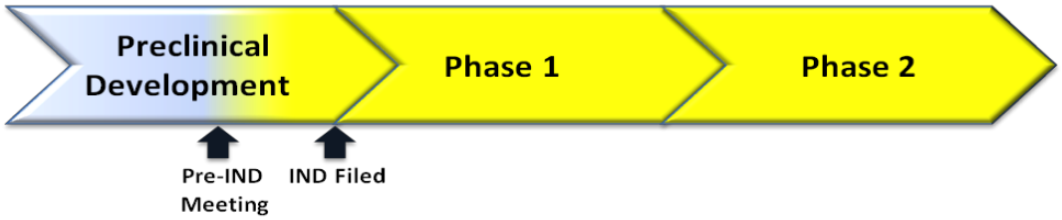
In addition, CIRM operates under special Public Records Act exemptions included in Proposition 71, the ballot initiative that created CIRM. Proposition 71 (Health & Safety Code, § 125290.30(e)(2)(B)-(C)) exempts from disclosure:

i. 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.

ii. 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	• Develop scalable process to support preclinical and first in human clinical studies • Make and/or release Master and Working Cell Banks • Assay development and qualification • Lock down final process • Finalize release criteria • Release GLP lot • Release GMP lot(s) • Stability studies	• Complete scale-up process development for future studies • Select potency assay • Manufacture GMP lots for Phase II	• 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 assays	• Complete comparability studies • Demonstrate comparability of product made with original versus scale-up processes	

Clinical/Reg	• Develop clinical strategy • Conduct pre-pre IND meeting (if not already held) • Conduct pre-IND meeting (if not already held) • 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 II protocol	• Initiate clinical site(s) • Enroll first patient • Complete Interim enrollment milestones • Last patient in • Data base lock

RFA 13-01 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**. If funded, milestones will be discussed with CIRM and modified as appropriate.

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	Q1 2016	Progress	

	15. Validate potency assay	Q2 2016	Progress	
Pharm/tox				
Clinical/ Regulatory	16. complete clinical study report			

RFA 13-01 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>

RFA 13-01 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

RFA 13-01 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