CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Memorandum

To: Members of the ICOC
From: Rosa Canet-Avilés, Chief Science Officer
Re: Revision to Preclinical Development (PDEV) Concept Presentation
Date: March 27, 2025

Please be advised that the former slide 56, summarizing PDEV Concept design, has been removed for brevity.

PDEV Funding Opportunity: Concept Overview

March 27, 2025

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PDEV I Outline

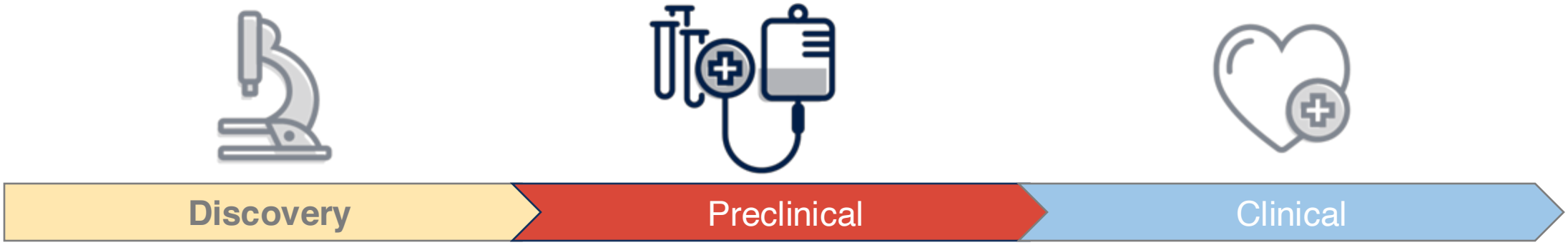
1. Background (SAF alignment)
2. Program Design Context
3. Objective
4. Scope
5. Structure
6. Timeline
7. Request for Motion

SAF Recommendations (Preclinical Development)

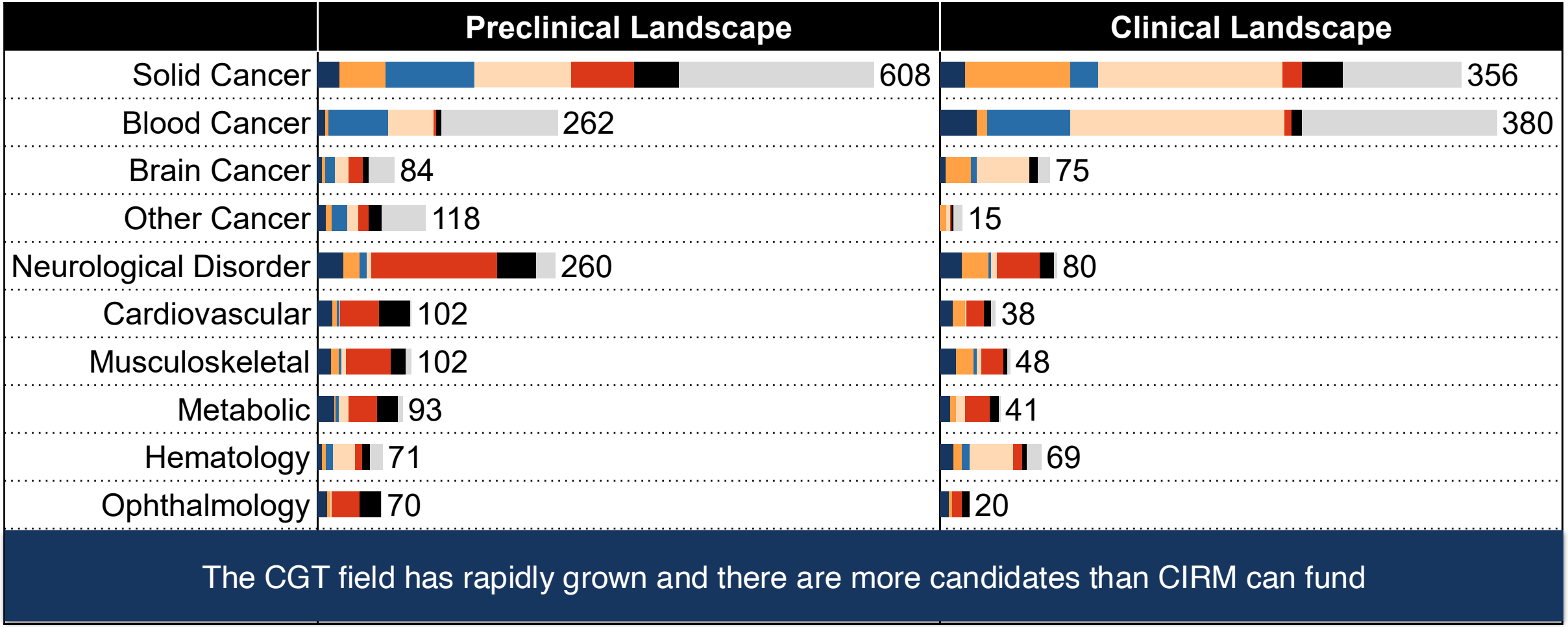
Goal 4 - Propel 15-20 therapies targeting diseases affecting Californians to late-stage trials

Streamline Preclinical Development Programs

- **Consolidate DISC2, TRAN1-4, and CLIN1** to accelerate the preclinical development incentivizing multidisciplinary collaborations and rapid progression to IND
- Incorporate **prioritization of innovative therapies for diseases that affect Californians**



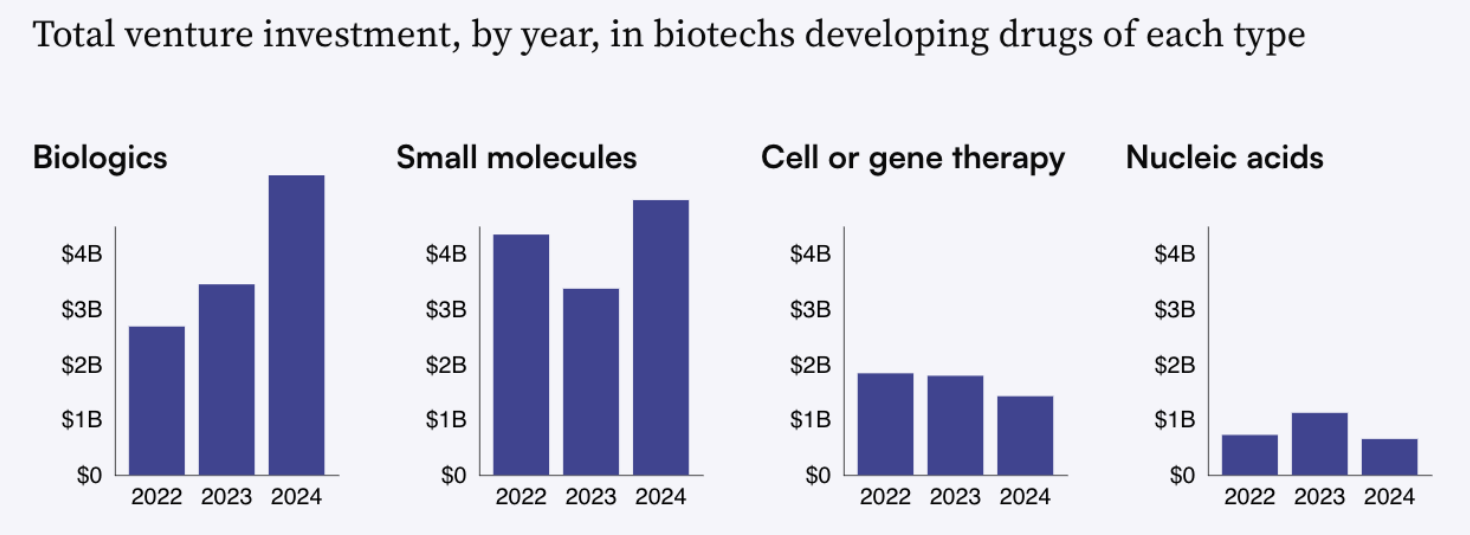
CGT External Landscape



GlobalData February 5, 2025 (Clinical includes US Phase 1, 2, 3)

Investment Landscape

Investment in CGT has flatlined & investors prioritizing clinical stage companies



"Biopharma **venture investments concentrated on clinical-stage** companies, resulting in higher median investment amounts"

-JP Morgan 2024

CIRM Partnering - 2024:

Despite **$2.2B** in industry support to CIRM-funded programs, only **~$60M went to preclinical**-stage companies

Sources: Biopharma Dive VC Tracker; JP Morgan 2024 Biopharma Industry Insights

Need for Holistic Preclinical Development Acceleration

CGT programs hold pre-IND meetings earlier in preclinical development

Multiple TRAN1 awards have **progressed to pre-IND meeting earlier than expected**, requiring award amendments to use their remaining funding to conduct studies informed by FDA feedback

Median **lag time** from Pre-IND meeting to CLIN1 award start: **~16 months**

Gene therapies may require **optimization of components**

Applications **within 6-12 months of pre-IND meeting** don't fit in TRAN1 or CLIN1

Consolidating preclinical development programs will enable a **holistic approach to acceleration**

Other Funding Agencies Provide Various Entry Points

Funding Agencies are increasingly developing funding mechanisms to support projects spanning multiple classical stages of therapeutic development

Funder	Program	Scope			
		Lead Optimization	*Pre-IND Meeting*	*IND Filing*	*FIH Trials*
FNIH/NIH	AMP – Bespoke Gene Therapy Consortium		✓	✓	✓
NIH	IND-enabling Studies of Somatic Gene Editing Therapeutic Leads	✓	✓	✓	
NIH	Blueprint Neurotherapeutics Network for Biologics	✓	✓	✓	✓
NIH	NHLBI Catalyze Program	✓	✓	✓	
CPRIT	Product Development Research Program		✓	✓	✓

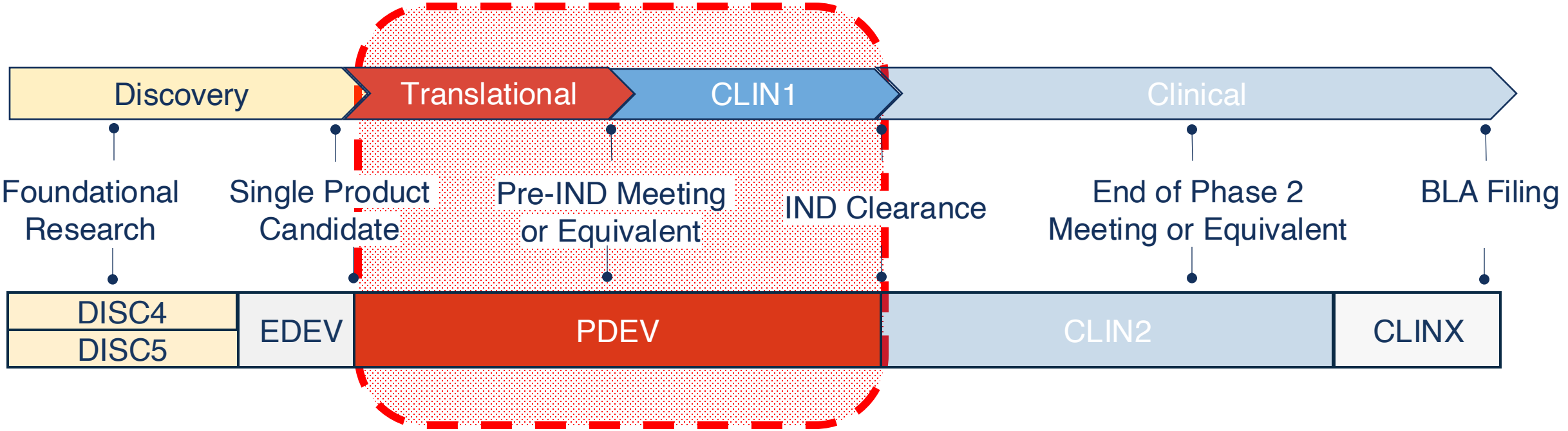
Note: All listed programs support cell therapies and/or genetic therapies

PDEV I Objective

Accelerate completion of **preclinical** development, FDA **IND clearance**, and clinical trial startup for **stem cell-based and genetic therapies**

PDEV I Overview

PDEV combines TRAN1 and CLIN1 into one program with a singular objective of accelerating stem cell-based and genetic therapies to first-in-human clinical trials



Recall I SAF Recommendations (Preclinical Development)

Goal 4 - Propel 15-20 therapies targeting diseases affecting Californians to late-stage trials

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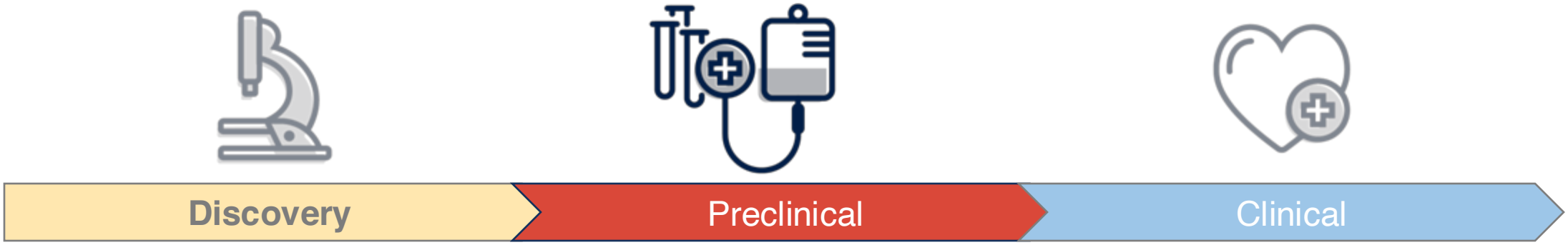
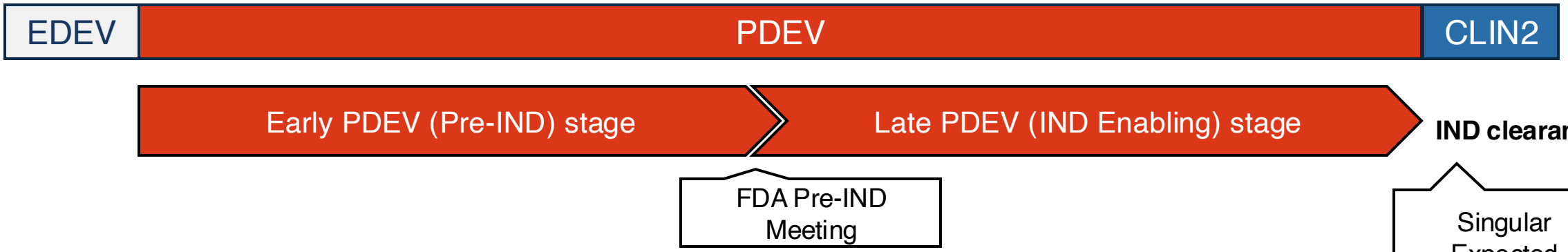


PDEV I Flexible Entry Points with a Single Outcome

PDEV covers critical pre-clinical development activities from candidate optimization to trial startup

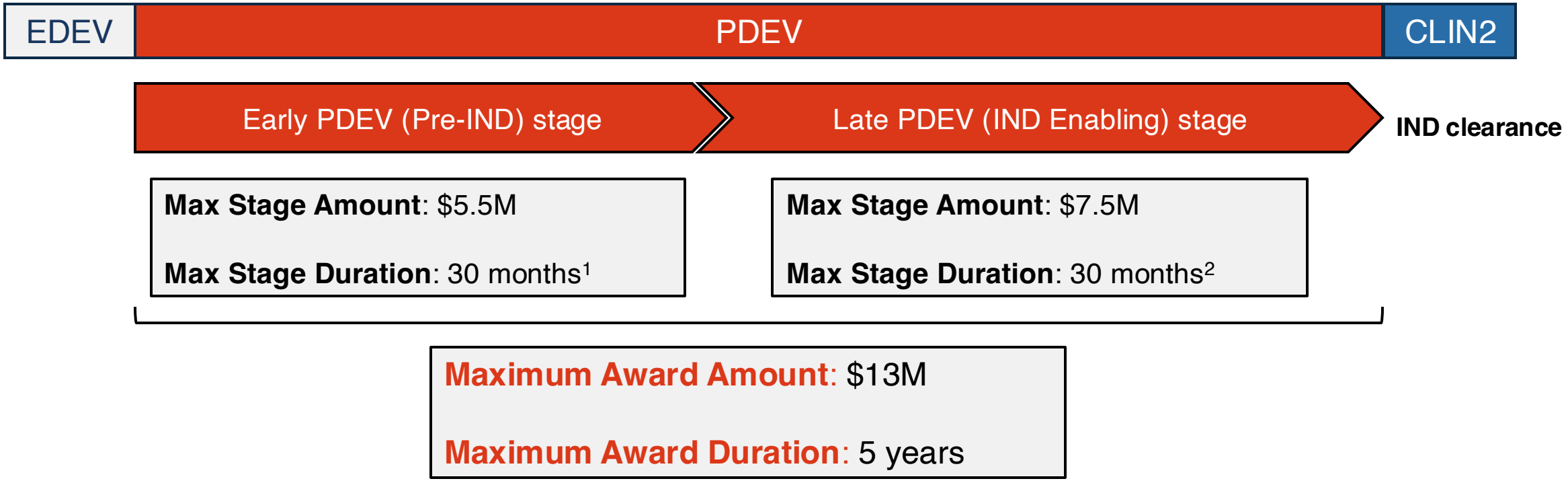


Illustrative activities *(non-exhaustive)*

CMC	Candidate optimization, formulation, process development	GMP manufacturing of DS & DP, analytical assay development & qualification
Nonclinical	Pilot dose range finding, pilot safety/ toxicology studies, efficacy studies	GLP safety / toxicology studies
Clinical	Clinical plan development/draft protocol, access planning	Clinical protocol development, trial start-up activities, access planning
Regulatory	INTERACT & Pre-IND package development	IND package development

DS = Drug Substance; DP = Drug Product

PDEV I Award Amount & Duration Varies by Entry Points



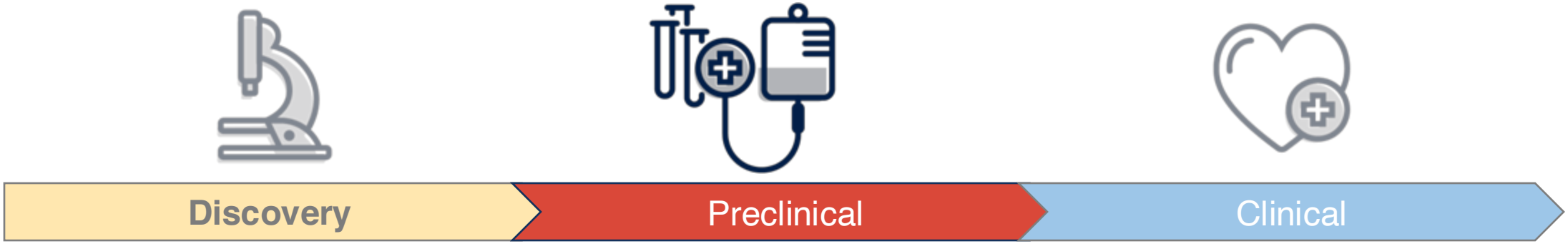
[1]Inclusive of optional candidate optimization activity (max 6 months)
[2]Inclusive of optional trial startup activity completion following IND clearance (max 6 months)

Recall I SAF Recommendations (Preclinical Development)

Goal 4 - Propel 15-20 therapies targeting diseases affecting Californians to late-stage trials

Streamline Preclinical Development Programs

- Consolidate DISC2, TRAN1-4, and CLIN1 to accelerate the preclinical development incentivizing multidisciplinary collaborations and rapid progression to IND
- **Incorporate prioritization of innovative therapies for diseases that affect Californians**



PDEV I Prioritizing to achieve SAF Goal

SAF Goal: Propel 15-20 therapies targeting diseases affecting Californians to late-stage trials

To achieve the SAF goal, the PDEV Program will incorporate program preferences

Guiding Principles:

- Fund therapies that
  - Offer potential for transformative clinical impact
  - Address bottlenecks to access and affordability
  - Are not adequately supported by federal funding or private investment

Implementation Plan:

- Build a diverse portfolio of therapeutic approaches
- Priorities informed by internal portfolio and external landscape analyses
- Approved on a fiscal year basis by the ICOC

PDEV I Preferences for FY25/26

Preferences will be factored in during pre-submission and ARS review

Concept Preferences	Rationale
Pluripotent stem cell-derived therapies	• Propositions 71 and 14 • Potential to address patient access & affordability barriers
In vivo genetic therapies	• Potential to address patient access & affordability barriers
Non-viral nucleic acid delivery	• Potential to address patient access & affordability barriers
Diseases of the brain and CNS (Prop 14)	• Proposition 14 priority
Progression from DISC2 & TRAN1 Awards	• Advance CIRM-funded therapies
Pre-IND or INTERACT meeting conducted	• Accelerate to IND clearance

PDEV I Application & Review

PDEV will incorporate a pre-submission process to:

- Manage high application volumes
- Reduce burden for applicants
- Implement program preferences
- Allow CIRM preplanning for improved scientific review

PDEV I Pre-submission Process Workflow

1 Pre-submission

Applicant completes a short pre-submission form in GMS (estimate ~60 per cycle)

2 CIRM Reviews

CIRM filters & rank orders pre-submissions based on preferences and related objective criteria

3 Full Application

PDEV program invites select applicants to submit full application

PDEV I Pre-Submission Rubric

Criteria		Key Considerations
1	**Prop 14 Preferences**	• PSC-derived therapies, in vivo gene therapies, diseases of the brain and CNS
2	**Other Preferences**	• Non-Viral Nucleic Acid Delivery • Pre-IND Meeting Conducted • Progression from DISC2 or TRAN1
3	**Under-represented therapeutic/disease area**	• Targeting a therapeutic/disease area under-represented in CIRM active awards portfolio
4	**Novelty of therapeutic approach**	• Differentiation compared to CIRM active awards portfolio

PDEV I Program Structure

	PDEV
Recurrence	2x / year
Max Award Duration	5 years
Applicant	California non-profit or for-profit research institutions
Co-funding[1]	20% (cash based or warrants based)
Max Award (total cost)	$13M (Total Project Cost)
Awards/Year[2]	12-21
Projection	7 Early-PDEV awards (7x$13M) & 9 Late-PDEV awards (9x$7.5M)
Total Funds/Year	$160,000,000

[1]Required for for-profit applicants and nonprofits applicants with for profit partners
[2] Number of awards that can be funded is dependent on proportion of Early & Late PDEV awards

PDEV I Eligibility

	Eligibility Requirements
Applicant	• California organization
Eligible Candidates	• Stem cell-based cell therapies and genetic therapies
Candidate Readiness	• Demonstrated disease modifying activity with candidate (same as TRAN)
Expected Outcome	• Must propose activities to achieve clearance of IND submission
Award Start	• Must be ready to start within 90 days of award approval
PI/PM Effort	• PI – 15% average maintained through duration of award • PM – 50% average maintained through duration of award
Co-Funding[1]	• 20% Total Allowable Project Costs (Cash-based or Warrants-based co-funding)

[1]Required for for-profit applicants and nonprofits applicants with for profit partners

PDEV I Access & Data Sharing Requirements

Require Access & Affordability Planning

- Awardees will be required to propose patient access and affordability planning activities

Data Sharing

- Require Data Sharing and Management Plan and coordination with CIRM's data initiatives

CIRM Network Knowledge Sharing

- Require and facilitate pre-competitive sharing between PDEV awardees on best practices for regulatory interactions, study designs, assay development, etc.

PDEV I Proactive Award Management

Proactive Award Management

- Increase real-time interactions between CIRM and awardee project teams
- Incorporate progress reporting from process development / GMP manufacturing leadership
- Inclusion of CIRM in FDA meetings
- External Product Development Expert Network will support CIRM Science Officers and project teams to accelerate projects to IND clearance

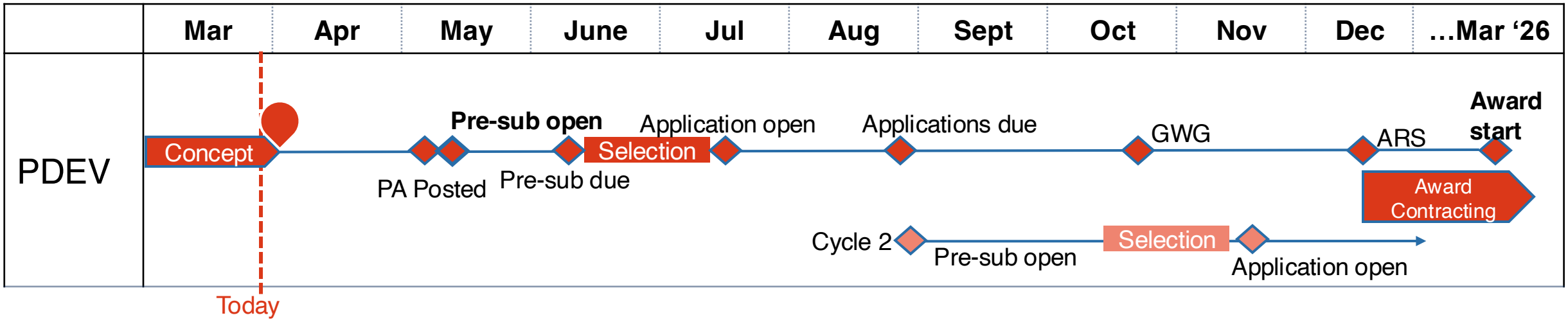
Acceleration & Performance Driven Milestone Structure

- Adopt CLIN1 Operational Milestone-driven award management. Delay of more than 4 months on an Operational Milestone triggers award termination review
- Require proactive communication on timely achievement of milestones and mitigation of project delays

PDEV I First Cycle Timeline

Pre-submission to award starts ~ 10 months

First cycle awards start in March 2026



Request for Motion

CIRM requests the ICOC approve the proposed PDEV Concept Plan