CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Grants Working Group Recommendations

CLIN2 Clinical Trial Awards

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Agenda

1. CLIN2 Program Overview
2. Review Process
3. Recommendations

Strategic Impact Goals

Accelerating Discovery & Translation	Cell & Gene Therapy Approvals	Accessibility & Affordability of Therapies	Diverse Workforce Development
Goal 1: Catalyze the identification and validation of at least four novel targets and biomarkers, ensuring integration into preclinical or clinical research for diseases in California **Goal 2:** Accelerate the development and utilization of 5-8 technologies that have the potential to improve safety, efficacy, and/or quality of cell and gene therapies	**Goal 3:** Advance 4-7 rare disease projects to Biologics License Application (BLA) **Goal 4:** Propel 15-20 therapies targeting diseases affecting Californians to late-stage trials	**Goal 5:** Ensure that every BLA-ready program has a strategy for access and affordability	**Goal 6:** Bolster CIRM's workforce development programs to address gaps and meet evolving demands in regenerative medicine

Strategic Impact Goals

Accelerating Discovery & Translation	**Cell & Gene Therapy Approvals**	Accessibility & Affordability of Therapies	Diverse Workforce Development
Goal 1: Catalyze the identification and validation of at least four novel targets and biomarkers, ensuring integration into preclinical or clinical research for diseases in California	**Goal 4:** Propel 15-20 therapies targeting diseases affecting Californians to late-stage trials	**Goal 5:** Ensure that every BLA-ready program has a strategy for access and affordability	**Goal 6:** Bolster CIRM's workforce development programs to address gaps and meet evolving demands in regenerative medicine
Goal 2: Accelerate the development and utilization of 5-8 technologies that have the potential to improve safety, efficacy, and/or quality of cell and gene therapies			

Updated CLIN2

- Allows for support of emerging **novel clinical trial designs** in CLIN2 program
- Incentivizes stage-appropriate **market access strategy** development and **pre-commercialization** activities in CLIN2 program
- Incorporates **prioritization of innovative therapies for diseases that affect Californians**

CLIN2 Program Objective

To support the completion of an interventional phase 1, 2, or 3 trial for an innovative stem cell-based or genetic therapy addressing a serious unmet need and with the potential for transformative benefits to patients, families and the health care system.

Evie Jr was born with sickle cell disease. He participated in a CIRM-funded trial at UCLA.

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CLIN2 Program Structure

	CLIN2		
	First-in-Human	Phase 2 or subsequent*	Phase 3 or pivotal
Recurrence	*4x per year*		
Max Duration	4 years		
Applicant	California or non-California organizations		
Co-funding**	30% (for-profit) None (non-profit)	50% (for-profit) None (non-profit)	50%
Max Award (Total Cost)	$8M (for-profit) $12M (non-profit)	$15M	$15M
Awards/Year	9-16***		
Projection	9 x $15M = $135M		
Total Funds/Year	$135M		

* Subsequent trials are Ph1 trials following a First-in-Human trial with the same candidate, disease indication and route of administration
** Co-funding is a percentage of total Allowable Project Costs
*** Number of awards is dependent on how many at each stage and organization status.

Review Process

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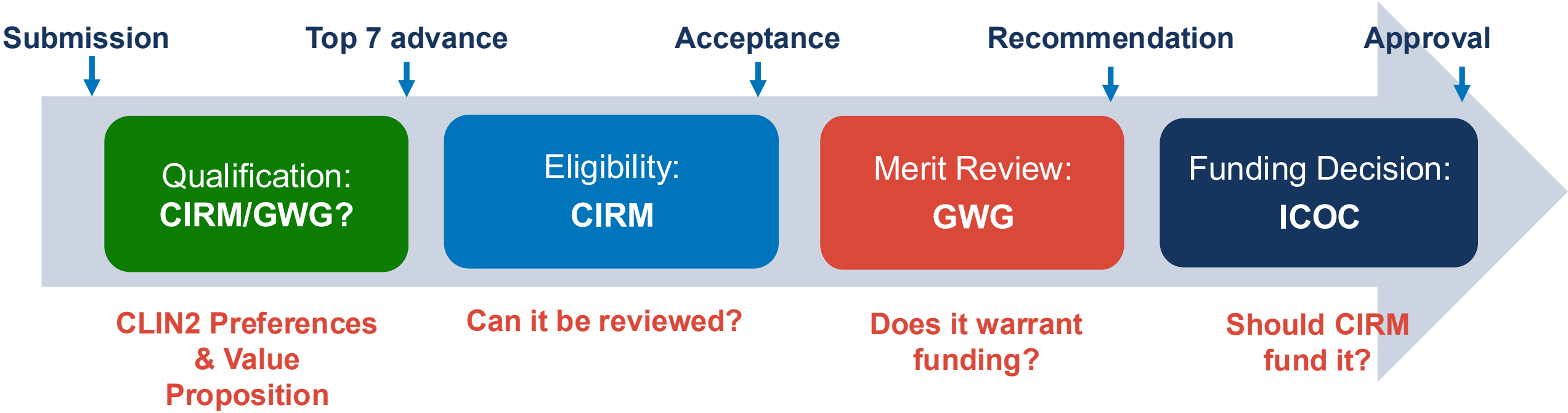
CLIN2 Application and Review Process



4 cycles per year (quarterly)

GWG – Grants Working Group; ICOC – Independent Citizens' Oversight Committee

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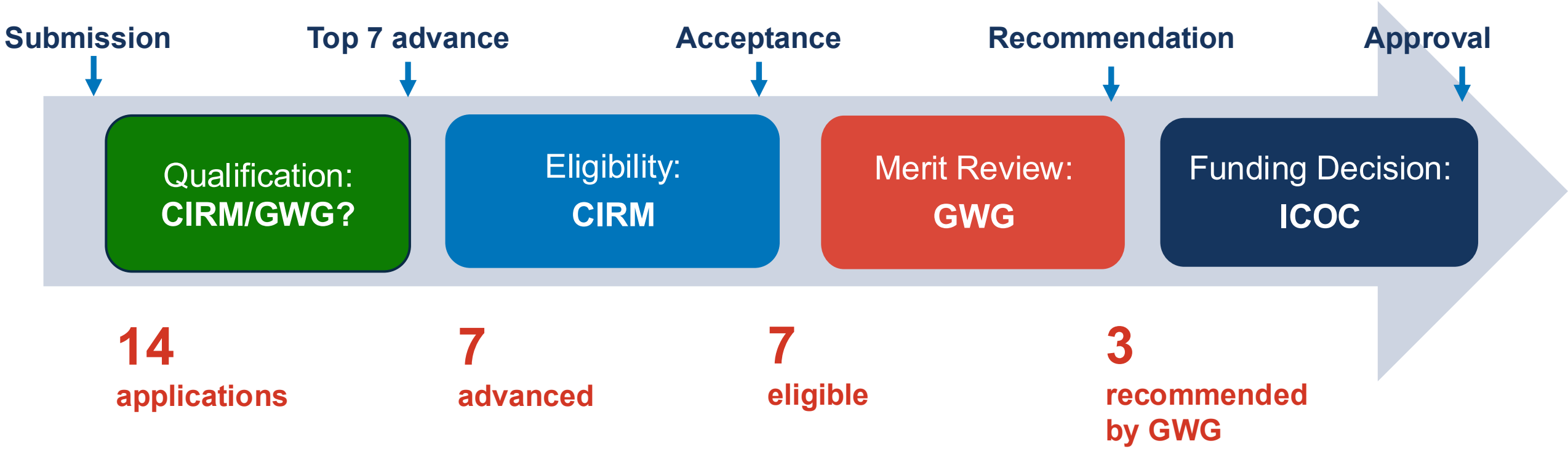
CLIN2 Application and Review Process



GWG – Grants Working Group; ICOC – Independent Citizens' Oversight Committee

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CLIN2 GWG Panel Composition and Roles

Who participates and how they contribute

Scientific GWG Member → Scientific evaluation (disease area expert, regulatory, CMC, Clin-Ops)

Access & Affordability Expert → Access and affordability evaluation

GWG Board Member → Patient perspective on significance and potential impact, oversight on process

Scientific Specialist → Scientific evaluation based on specialized expertise

Scientific Scoring System

Using the 1 to 100 scale

- **Median score of 85-100:** Exceptional merit and warrants funding, if funds are available.
- **Median score of 1-84:** Not recommended for funding.
- Scoring is holistic and based upon all facets of the expert review.
- GWG are encouraged to make full use of the scoring range to signal their enthusiasm for each project.

CLIN2 Scientific Review Criteria

- **Value Proposition** - Evaluate the extent to which the therapy offers a compelling value proposition
- **Rationale** - Evaluate the scientific rationale for the proposed therapy and the strength of the supporting data
- **Project Plan and Design** - Evaluate the project's plan and design
- **Project Team and Resources** - Evaluate the expertise and resources that will be deployed to achieve the project deliverables
- **Population Impact** – Evaluate the extent to which the project considers the potential impact of the proposed therapy across affected populations

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Recommendations

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GWG Recommendations

Recommendation	Number of Apps	Total Applicant Request	Funds Available
Recommended for funding	3	$20,928,438	$61,000,067
Not recommended for funding	2		

For each award, the final award amount shall not exceed the amount approved by the ICOC Application Review Subcommittee and may be reduced contingent on CIRM's assessment of allowable costs and activities.

Minority Reports

- Under Prop 14, any application that is not recommended for funding by the GWG, but which had 35% or more members score to fund the application must include a minority report.
- The minority report is included in the review summary and provides a brief synopsis of the opinion of reviewers that scored the application 85 or above.

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Applications with Minority Report

The CIRM Team supports the majority position to not fund application CLIN2-20117.

App Number	Title	Funds Requested	Score
CLIN2-20117	A Phase I/IIa, Dose-Escalation Study for the Treatment of Focal Articular Cartilage Defects in the Knee	$11,193,750	80

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CIRM Team Recommendations

CIRM Team concurs with GWG recommendations for funding

App #	Budget Request	GWG Score	Lo	Hi	Y	N	CIRM Recommendation
CLIN2-19848	**$8,000,000**	**94**	84	95	13	1	**FUND**
CLIN2-19928	**$4,928,664**	**88**	75	92	10	3	**FUND**
CLIN2-19526	**$7,999,774**	**85**	80	90	12	2	**FUND**

Total Applicant Request	Funds Available
$20,928,438	$61,000,067

For each award, the final award amount shall not exceed the amount approved by the ICOC Application Review Subcommittee and may be reduced contingent on CIRM's assessment of allowable costs and activities.

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CLIN2-19848

A Phase 1/2a First-in-Human, Dose-Escalation Study in Subjects with Progressive Multiple Sclerosis

Therapy	Trial Phase	Prior Funding to Team
Allogeneic CAR-Treg	Phase 1/2a	Yes

CIRM Team Recommendation: **Fund**
Rationale: GWG score, strong patient access planning, portfolio indication diversification, and novel therapeutic approach compared to the external landscape

Summary:

	Assessment
Transformative Clinical Impact	Differentiated approach to unmet medical need
Patient Access	Modality choice and delivery can meaningfully expand access; well developed, stage-appropriate plan
Disease Representation	Multiple Sclerosis is a prevalent neurological disease not present in CIRM's PDEV or CLIN2 portfolio

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CLIN2-19928

Phase 1/2 Study of an AAV-9 Gene Therapy in Patients with FOXG1 Syndrome

Therapy	Phase	Prior Funding to Team
AAV9-delivered *FOXG1* gene	Phase 1/2a	No

CIRM Team Recommendation: **Fund**
Rationale: GWG score, strong patient-centered development and access planning, portfolio indication diversification, indication has no known external development programs

Summary:

	Assessment
Transformative Clinical Impact	High potential for meaningful clinical outcomes; no other known therapies in development
Patient Access	Stage-appropriate, patient-centered approach has been integrated in development plan
Disease Representation	FOXG1 syndrome is an ultra-rare disease not present in CIRM's portfolio

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CLIN2-19526

AAV Immuno-Gene Therapy for High-Grade Glioma

Therapy	Phase	Prior Funding to Team
AAV-delivered interferon beta	First-in-Human	Yes

CIRM Team Recommendation: **Fund**
Rationale: GWG score, novel therapeutic approach in portfolio and novel therapeutic approach compared to external landscape

Summary:

	Assessment
Transformative Clinical Impact	Immunotherapy approach is agnostic to tumor subtypes. Although CIRM's portfolio contains 5 active CLIN2 awards addressing glioma and there are 49 known external clinical programs, this approach is novel.
Patient Access	Proposed activites were stage appropriate but focused on California
Disease Representation	Gliomas are rare brain cancers. Approximately 10% of CIRM's active CLIN2 awards address brain cancer (5 awards).

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CLIN2-20117

A Phase 1/2a Dose-escalation Study for the Treatment of Focal Articular Cartilage Defects in the Knee

Therapy	Phase	Prior Funding to Team
Allogeneic, hPSC-derived articular cartilage-like cell implant	Phase 1/2a	Yes

CIRM Team Recommendation: Do not fund
Rationale: GWG Score

Summary:

	Assessment
Transformative Clinical Impact	The therapy addresses a subset of the population for whom the unmet need may not be urgent, cartilage repair technologies are available
Patient Access	The patient access plan is stage appropriate; however, the addressable population differs from the broader osteoarthritis/cartilage repair population and this must be addressed to develop a well-informed access plan
Disease Representation	Focal articular cartilage defect is an indication not present in CIRM's portfolio[21]