January 6, 2026

Open Letter to the U.S. Food and Drug Administration

To: FDA Officials, Policymakers, and Rare Disease Stakeholders
From: Haystack Project's Patient Advocacy Organizations Regarding the RDEP Process

Introduction

Recently the Rare Disease Evidence Principles (RDEP) framework was announced -- in the middle of a Rare disease Innovation, Science and Exploration (RISE) workshop and under the auspices of the "Rare Hub" – got the expected support from stakeholders not living with or caring for a loved one impacted by a rare disease. Rare disease patients, parents, and caregivers hoping for a treatment, however, understand that this "better than nothing" effort sells our lives and families short.

Yes, we appreciate FDA wants to "do more" for rare diseases and are aware of all the interviews, podcasts, and conferences highlighting the unique challenges inherent to rare disease research and development (R&D). While we applauded the FDA's approval of the first ever treatment for Barth Syndrome - it is important to also understand the cost. The Barth Syndrome Foundation undertook herculean advocacy efforts through 3 submissions and 4 review divisions. But it should not be that hard, nor should they have had to mourn the loss of 18% of their community in the process. Would the RDEP framework fix the problems that frustrated the Barth Syndrome community and nearly bankrupted the research sponsor? In its current state, it still would not have been enough to ensure more timely approval.

For our communities, the biggest problem with the RDEP is ***not*** that it misses the mark on solving ***all*** of the problems ultra-rare R&D sponsors and patients face. It is the high potential that the RDEP's narrow applicability will create more risk, confusion and uncertainty than it relieves.

RDEP eligibility is limited to conditions that are (1) caused by a known, in-born genetic defect; (2) rapidly progressive to disability or death within a short time; and (3) impact 1,000 or fewer patients. The studied treatment must either correct the gene or replace an essential physiological protein that is deficient due to the genetic defect. The "benefits" of the RDEP for qualifying programs would be regulatory flexibility in, for example, accepting single-arm studies (with a requirement for post-approval confirmatory evidence as needed). We do not need the RDEP layer of bureaucracy - single-arm studies are not only

acceptable for rapidly fatal or disabling conditions, they were (and still are) often the only ethical way to study a new treatment. Randomization to a control arm in the absence of an alternative therapy is unethical if there is another way to determine treatment effect. Especially since the RDEP criteria require/assume sufficient natural history evidence (rapid progression over a short time) to rely on historic comparators as a control. Is FDA going to rigidly insist on randomized controlled trials (RCT) in rapidly progressive fatal/disabling conditions outside the RDEP?

The RDEP also promises increased transparency and interaction with FDA and its reviewers. Isn't that ***already*** the promise of the Orphan Drug Act, or designation as Breakthrough Therapy, or Regenerative Medicine and Advanced Therapies (RMAT)? We have seen the interminable journey in bringing a Barth Syndrome treatment to patients in combination with the recently issued Complete Response (or Refusal to File) Letters for other rare and ultra-rare disease treatments. How eager will innovators and investors be to pursue R&D in conditions like galactosemia, ARG-1D, and other very rare conditions with slow progression and heterogeneity?

We have repeatedly urged FDA to recognize the mathematical fact that randomization can be an extremely risky, inadequate, and insufficient control mechanism. Too many rare disease R&D programs will continue to fail due to trial designs that are not the right tool for the job of assessing safety and efficacy when disease progression is slow and variable. Our patients and families will continue to suffer and, eventually, even if a therapeutic approach is discovered, it will languish "on the shelf" with the 1,000+ other abandoned rare disease R&D programs.

Haystack Project recently brought together leading rare disease experts from across the country to identify the "problem(s)" and present recommendations for refinements that would not require legislative change and would enhance scientific rigor through fit-for-purpose study designs. These recommendations are outlined in the white paper entitled "Redefining Rigor: Fit-for-Purpose Trials to Unlock Rare Disease Therapies" and urge FDA to:

- Use an operational definition of "well-controlled investigations" to reflect the rare disease reality that randomization may be a poor control method in conditions with slow progression, significant heterogeneity, and small populations
- Replace "regulatory flexibility" discretion with clearly outlined examples of alternative methodologies and innovative designs that can constitute well-controlled investigations
- Reduce the burden and unpredictability associated with biomarkers as surrogate endpoints
- Emphasize the importance of disease-specific experience/expertise in rare disease study design, endpoint selection, data analysis, and evaluation
- Move away from the "hypothesis testing" approach that tends to "doom" many rare disease R&D programs in favor of alternative statistical analysis plans

We urge the FDA to reconsider the RDEP and its narrow approach – its benefits do not seem to outweigh its risks. What we need is a regulatory framework that eschews the inquiry on whether an RCT is "feasible" in favor of the critical question the statute demands – what study design is likely to yield a "well-controlled investigation."

We invite FDA officials to join us in dialogue and commit to policies that address the full spectrum of challenges in rare disease research and development. Our patients and caregivers deserve no less.

Sincerely,
AIM at Melanoma
Association for Creatine Deficiencies
Biomarker Collaborative
CDG CARE
Chondrosarcoma Foundation
Coalition to Cure Calpain 3
CTNNB1 Connect and Cure
Cure GM1 Foundation
Cure LGMD2i Foundation
Cutaneous Lymphoma Foundation
Exon 20 Group
FACES: The National Craniofacial Association
Facial Pain Association
FCS Foundation
Galactosemia Foundation
Hope for Stomach Cancer
HypoPARAthyroidism Assoc
ICAN, International Cancer Advocacy Network
International Fibrodysplasia Ossificans Progressiva (FOP) Association
International Pemphigus & Pemphigoid Foundation
LGMD Awareness Foundation, Inc
LGMD2D Foundation
LGMD2L Foundation
Luka Shai Foundation
MET Crusaders
MitoAction
MLD Foundation
Muenzer MPS Center
Myasthenia Gravis Foundation of America
National Leiomyosarcoma Foundation
NPHP1 Family Foundation
NTM Info & Research
Organic Acidemia Association

PDL1 Amplifieds
Rein in Sarcoma
Sarcoma Foundation of America
Share and Care Cockayne Syndrome Network Inc
SLC6A1 Connect
Speak Foundation
Sudden Arrhythmia Death Syndromes Foundation
Taylor's Tale
The Desmoid Tumor Research Foundation
The Global Foundation for Peroxisomal Disorders
The Sturge-Weber Foundation
Usher 1F Collaborative