REAGAN-UDALL FOUNDATION FOR THE FDA

Recommendations for Expanding Regulatory Agility and Evidentiary Integrity in Developing Treatments for Rare Diseases

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REAGAN-UDALL FOUNDATION FOR THE FDA

About the Reagan-Udall Foundation for the FDA

The Reagan-Udall Foundation for the FDA (Foundation) is an independent non-profit created by congress to advance regulatory science to help the U.S. Food and Drug Administration accomplish its mission. The Foundation manages a suite of programs that assist the FDA in engaging with external stakeholders and that facilitate evidence generation, improve public understanding of the FDA, and deliver more accessible health information to the public.

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EXECUTIVE SUMMARY

In January 2026, the Reagan-Udall Foundation for the FDA convened an invitation-only Roundtable with representatives from medical research, patient organizations, regulatory agencies, and regulated industry. The discussions focused on advancing shared understanding of patient-relevant endpoints and explored practical pathways for expediting rare disease clinical development that is meaningful to patients. Participants acknowledged that existing guidance and methodological frameworks illustrate that the development of endpoints and tools that align with patient priorities is achievable, although important questions about successfully operationalizing these approaches remain.

The Roundtable discussions focused on realistic, evidence-based strategies designed to improve patient quality of life while preserving endpoints that support credible, efficient, and feasible regulatory evaluation. The recommendations are actionable and designed to move patient-focused rare disease clinical development from principle to practice. A common theme from the meeting was the need for specific collaborations that address identified challenges. These collaborations would develop, publish, and disseminate issue-specific frameworks, case studies, and peer-reviewed publications that provide aligned understandings between regulators and stakeholders about the best paths forward. The recommendations are tailored to address the unique aspects of rare disease clinical development where evidence continues to build during clinical trials and small patient populations are often heterogeneous. Participants discussed the value of sharing information about successful approaches to developing patient-relevant endpoints and trial designs, including insights about the scientific principles and methodological approaches that enabled those successes. They also valued sharing those same insights for patient-centered approaches that failed. Lastly, the Roundtable participants identified areas where pre-competitive approaches could optimize data collection efforts and enable the use of disease-agnostic tools.

Specifically, the following topics were discussed: 1) Developing Regulatorily-Acceptable Patient-relevant Endpoints; 2) Optimizing Patient Perspective and Natural History Data Collection and Utilization; 3) Advancing Shared Understandings of Evidentiary Expectations and Regulatory Requirements; and 4) Importance of Cross-Stakeholder Knowledge Management. Within these topic areas, Roundtable participants identified 10 specific challenges and developed 20 actionable recommendations (See Appendix A: Table 1).

BACKGROUND

There are more than 10,000 known rare diseases that affect 30 million people in the United States. Yet, only 5% of these known diseases have a treatment approved by the U.S. Food and Drug Administration (FDA).[1] A majority of these diseases (70%) manifest in childhood with progressive or degenerative trajectories that substantially impact lifespan and quality of life.[2,3] Clinical heterogeneity is common in rare diseases with patients often presenting widely variable symptoms, disease severity, progression rates, and responses to interventions.[4] Thus in addition to the challenges of recruiting and powering clinical development studies for small patient populations, complex ethical considerations must be taken into account, and phenotypic heterogeneity complicates efforts to develop and evaluate clinical outcome measures.[5]

The development of novel medicines is a high-risk, time intensive, and costly endeavor.[6] Rare disease clinical development programs frequently require specialized trial designs, global site activation, and highly targeted recruitment strategies.[7] The operational complexity of identifying potentially eligible patients from geographically dispersed populations, recruiting and retaining small numbers of participants, activating and maintaining multinational clinical sites for small patient numbers, managing multiple compliance paradigms, and implementing specialized infrastructure for complex interventions such as gene therapy or enzyme replacement therapy often results in a significantly higher per patient clinical trial cost than seen in more common conditions.[7,8,9] Manufacturing challenges for cell and gene therapies, enzyme replacement therapies, and other biologics commonly used in rare diseases also add financial and operational constraints.[10] Rare disease development is heavily shaped by perceived risk of investment, particularly for emerging biotech companies. Limited precedent and endpoint uncertainty increase investment risk and can halt potentially promising development programs.[a]

Historically, the United States has implemented a range of regulatory policies to stimulate orphan drug development and expand treatment options for rare diseases. For example, the Orphan Drug Act of 1983 established foundational incentives offering tax credits for clinical trials, waiving user fees, and providing 7 years of regulatory exclusivity. Additional policies, such as those outlined in the 21st Century Cures Act, including the Pediatric Rare Disease Priority Review Voucher program, further encourage the development of treatments for pediatric patients with rare conditions by authorizing the issuance of transferrable vouchers that can be redeemed to obtain expedited FDA review for another drug product, helping offset the financial and scientific challenges associated with orphan drug development for pediatric populations.[11,12]

[a] Adoption by payors is another essential step in ultimately treatments reaching patients. This Roundtable did not address payor policy; participants acknowledged the need for future discussions on how to better align regulatory and payor evidence requirements.

Building on this legislative foundation, FDA has established a cross-center Rare Disease Innovation Hub and advanced several initiatives and supporting activities to address the scientific, regulatory, and evidentiary challenges of rare disease development. These initiatives are summarized in Table 2 and are complemented by ongoing efforts across FDA to strengthen regulatory science, patient engagement, and internal expertise. Efforts include issuing guidance to encourage rare disease product development, conducting specialized training for FDA staff, awarding research grants and cooperative agreements, administering expanded access (i.e., compassionate use) programs, convening the FDA Rare Disease Council, and collaborating on agency-wide engagement efforts such as Rare Disease Day.

FDA also expanded stakeholder engagement through mechanisms, such as patient listening sessions, which provide direct opportunities for patients, caregivers, and advocacy organizations to share lived experiences, priorities, and unmet needs. These insights help FDA better understand what outcomes matter most to patients and can inform clinical trial design, endpoint selection, and benefit-risk considerations. Collectively, these legislative and regulatory efforts aspire to provide incentives, regulatory clarity, and market transparency intended to spur rare disease drug development.

While significant progress has been made in terms of the number of medicines approved by the FDA since the enactment of the Orphan Drug Act in 1983 (>800 approved rare disease medicines), natural history data suitable for regulatory decision making remains limited, knowledge about rare diseases varies, and a lack of precedence for utilizing newer, potentially more meaningful, clinical endpoints and trial designs often still exists.[13, 14, 15, 16, 17] Given the scientific challenges and operational complexities, it is paramount that regulators, medical researchers, patients, patient advocates, and clinical trial sponsors continue to work together to advance shared understandings about how to design trials, submit evidence packages best able to meet regulatory requirements, and provide patients with outcomes meaningful to them and their families.

Table 2. FDA Rare Disease Initiatives*

Initiative	Purpose / Description	Reference Source
Rare Disease Innovation Hub	Coordinates regulatory science, develops policy approaches, and provides consistency in reviews for rare disease products through a cross-center FDA effort Convenes rare disease experts, regulators, developers, and patients to address shared drug development challenges, foster collaboration, and explore innovative solutions with public, interactive discussions through Rare Disease Innovation, Science, and Exploration (RISE) Workshops	FDA Rare Disease Innovation Hub: https://www.fda.gov/industry/medical-products-rare-diseases-and-conditions/fda-rare-disease-innovation-hub https://www.fda.gov/industry/fda-rare-disease-innovation-hub/rare-disease-innovation-science-and-exploration-rise-workshop-series
Rare Disease Evidence Principles (RDEP)	Offers a clarified process for evidence generation in rare diseases, including flexibility when traditional randomized control trials are not feasible	FDA RDEP Webpage (2025): fda.gov/industry/fda-rare-disease-innovation-hub/cdercber-rare-disease-evidence-principles-rdep
Natural History Study & Real-World Evidence (RWE) Programs	Supports leveraging real-world evidence and natural history data to inform trial design, endpoint relevance, and patient heterogeneity	FDA Rare Disease Science Programs: fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development
Patient Listening Sessions	Offers direct engagement mechanism for patients and caregivers to inform FDA about disease burden, meaningful outcomes, and unmet needs	FDA Patient Listening Sessions: fda.gov/patients/learn-about-fda-patient-engagement/fda-patient-listening-sessions
Office of Orphan Products Development (OOPD) Programs	Provides grants, natural history grants, and regulatory support for advancing orphan drug development	FDA OOPD Overview: fda.gov/about-fda/office-chief-medical-officer/office-orphan-products-development
Accelerating Rare Disease Cures (ARC) Program	Supports the overview and coordination of Center for Drug Evaluation and Research's (CDER) rare disease activities and external communications	FDA CDER (2022): https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/accelerating-rare-disease-cures-arc-program
Rare Disease Cures Accelerator-Data and Analytics Platform (RDCA-DAP)	Provides a centralized platform for sharing patient-level data, developing data standards and tools for rare disease clinical development	FDA and Critical Path Institute (C-Path): https://c-path.org/program/rare-disease-cures-accelerators-data-and-analytics-platform/

* For information on additional rare disease programs, please see Appendices and 2024 GAO Report, FDA Has Steps Underway to Strengthen Coordination of Activities Supporting Drug Development.[18]

TOPIC 1

Developing Regulatorily-Acceptable Patient-Relevant Endpoints

CHALLENGE

Misaligned Validation and Qualification Timelines with Patient Needs

Among the most persistent challenges in rare disease clinical development is endpoint uncertainty, particularly the difficulty of defining and validating patient-relevant endpoints. Endpoint selection for medicines seeking traditional approval (21 CFR 314 subpart B) must reflect clinical benefit—how a patient feels, functions, or survives—consistent with FDA's Patient-Focused Drug Development (PFDD) framework.[19] A patient-relevant endpoint is an outcome directly tied to patient-identified disease burden. Given the heterogeneity of rare diseases, these can include an array of disparate concepts of interest such as motor decline, fatigue, swallowing difficulty, respiratory compromise, communication challenges, pain, or loss of independence. These concepts are typically identified through qualitative and mixed-method approaches such as concept-elicitation interviews, patient- and caregiver-reported data, patient listening sessions, and natural history studies.[20,21,22] To be used in a clinical trial, the patient-relevant concept of interest must be measured with a clinical outcome assessment (COA), such as a patient-reported, caregiver-reported, clinician-assessed, or performance-based measure, that is fit-for-purpose for rare-disease drug development. This requirement ensures that endpoints reflect what matters to patients while meeting FDA expectations for reliability, validity, sensitivity to change, and interpretability.[25,23,24] Thus sponsors and regulators must align on both context of use and concept of patient interest for endpoints evaluated in a clinical trial.

Each of these processes takes time, and time adds up. Roundtable participants cited examples where endpoint exploration and validation were ongoing late into the clinical development process. The FDA COA Qualification Program and broader Drug Development Tool (DDT) framework provide structured pathways for generating and evaluating evidence of COAs over time, even when full validation is not immediately achievable. However, these are also multi-year processes and are in need of re-evaluation and reform.[24] As of October 2024, the FDA has qualified seven COAs, with reviews taking an average of six years.[25] Further, sponsors often have to duplicate efforts to enable utilization and obtain validation from other regulatory authorities, such as the European Medicines Agency (EMA), adding additional time and cost. These timelines are prohibitive to advancing the use of patient-relevant endpoints and keeping pace with evolving medical knowledge. As rare disease clinical trials are a global endeavor, participants recommended the adoption of processes that enable more real-time collaboration and acceptance of patient-relevant endpoints by multiple regulatory authorities.

> *"We don't have seven years to validate something. Patients can't wait that long."*

RECOMMENDATION 1
Enable Mutual Recognition of DDT and Endpoint Qualifications

Sponsors and regulators from multiple regions should work together to advance mutual recognition processes for rare disease patient-relevant endpoint acceptance. The FDA and the EMA, for example, have historical precedents in accelerating access to validated tools in cross-border contexts. Conceptually, if an endpoint, biomarker, or DDT tool is formally qualified for a specific context of use (COU) by one authority, it may be reasonable to pursue expedited or simultaneous consideration or recognition by others. This concept aligns with harmonization efforts and joint scientific advice programs that seek to reduce duplication of effort, especially for rare diseases where development timelines are long and populations are small.

CHALLENGE
The "Precedent Paradox" That Limits Acceptance of Novel Approaches

Developing and using novel or modified endpoints increases both risk, or at least the perception of risk, and clinical development time for developers, regulators, and patients themselves. While risk aversion is improving, the perception of risk or perceived risk of longer development times often tips the scales in favor of existing endpoints already accepted by regulators. Participants discussed how this precedent paradox—weighing risk mitigation versus novel endpoints—is a barrier to utilizing more patient-relevant primary and secondary endpoints; it limits acceptance of, and interest in, novel approaches.

Sponsors facing finite resources and high-stakes investment decisions often default to previously accepted endpoints even when those measures may not be as relevant to patients as other novel endpoints. A rejected primary endpoint can delay or terminate a program, with limited opportunity for recovery in ultra-small populations where re-enrollment is impractical. This is an acute issue for emerging biopharmaceutical companies that have little to no revenue and small clinical development portfolios. As 63% of newly approved drugs in 2024 were originated and launched by emerging biopharmaceutical companies, overcoming these risk barriers will require a transparent and engaged regulatory environment.[26]

Participants emphasized that patient-relevant outcomes in rare diseases frequently involve complex, multidimensional constructs such as the maintenance of swallowing function, preservation of independent ambulation, reduction in seizure-related hospitalizations, pain reduction, or the ability to attend school, all of which do not map neatly onto existing validated instruments. In fact, recent analyses have shown that even when patient priorities are well

characterized, operationalizing those concepts into measurable endpoints often fails because existing tools lack sensitivity or do not align with the frequency or context of meaningful daily activities.[27,28] While several FDA and International Council of Harmonisation guidance documents acknowledge the importance of developing endpoints that matter to patients, turning these principles into practice continues to prove difficult.[23,29,30]

To break the precedent paradox cycle, and usher in widespread use of patient-relevant endpoints, other issues need to be addressed as well. For example, balancing the benefits of a regulatory environment that relies on precedent to ensure consistency and predictability in evidentiary standards with the needs and realities of developing medicines for rare diseases with little to no precedent is important. The FDA requires that primary endpoints exhibit:[31,32]

- Reliability (adequate test/retest stability, inter-rater consistency)
- Construct and content validity
- Sensitivity to detect within-patient change
- Statistical interpretability, including estimation of meaningful change
- Operational feasibility across sites and geographies

Matching this methodological rigor with what matters to patients is a difficult combination to achieve in ultra-rare, heterogeneous, or rapidly progressive diseases. As a result, rare disease endpoints are often chosen primarily for feasibility, standardization, or known regulatory precedent rather than for their alignment with patient-identified priorities. For example, reliance on biomarkers and other surrogate endpoints is common in rare metabolic and lysosomal diseases where functional outcomes are slow to change or difficult to measure within feasible trial durations and where biochemical or anatomical markers are often used to infer treatment effect.[33] The Accelerated Approval pathway enables the use of postmarketing confirmatory studies to confirm benefits for surrogates that lack fully validated correlations with functional improvements at the time of approval.[21,34,35] It should not be inferred, however, that the use of biomarkers and surrogate endpoints are not meaningful to patients. The use of biomarkers able to serve as a direct measure of the core underlying primary biology is an important field to advance, as these biomarkers would provide support for biologic plausibility and development treatments that target the cause of the disease before symptoms progress.[36] It is connecting these biomarkers with patient-relevant endpoints that can be the challenge.

There are several examples where commonly used rare disease endpoints reflect a trade-off between feasibility and patient relevance (Table 3). The Six-Minute Walk Test (6MWT) is widely used in rare neuromuscular diseases, such as Duchenne muscular dystrophy (DMD), because it is standardized, reproducible, and sensitive to ambulatory decline. However, it fails to capture domains that patients and families identify as more meaningful such as endurance, fatigue, and upper extremity function.[37,38] Forced vital capacity (FVC), a core endpoint in Amyotrophic Lateral Sclerosis (ALS) and other neuromuscular disorders, is reproducible and correlates with survival, but it is an incomplete marker of patient burden because it is poorly sensitive to early inspiratory muscle weakness, may miss early nocturnal hypoventilation, and does not capture bulbar

problems, such as speech and swallowing difficulties or respiratory fatigue, that patients often describe as more troubling than spirometric decline.[39, 40, 41] Similarly, spleen volume reduction in myelofibrosis and Gaucher disease is an objective and precise anatomical measurement, but often correlates poorly with symptom relief, including pain, satiety, and fatigue.[42, 43, 44] Timed motor function tests (TFTs) provide reliable assessments of gross motor performance and can be prodromal of latter functional loss, yet they suffer from limited understanding of their reflection of real-world impact on patient function, developmental variability, and floor or ceiling effects, particularly in progressive neuromuscular disorders.[45, 46, 47]

FDA's Rare Disease Endpoint Advancement pilot program, established in 2022 under Prescription Drug User Fee Act VII (PDUFA VII), is working to advance learnings about how to develop novel endpoints that are meaningful to patients.[48] However, if the regulatory risk of proposing a novel measure for rare disease clinical programs continues to be perceived as prohibitively high, a self-reinforcing cycle of using familiar, but suboptimal, endpoints will remain. Roundtable participants conveyed that collaborations between stakeholders and regulators focused on developing innovative approaches to develop endpoints that meet context of use, patient interest, and regulatory expectations are needed.

Table 3. Rare Disease Endpoint Precedents: Measurement Strength vs. Patient Centered-Limitation

Endpoint	Rare Disease Application	Regulatory Strength	Patient-Centered Limitation
6-Minute Walk Test (6MWT)	DMD, metabolic myopathies	Standardized performance outcome assessment (PerfO); sensitive to early ambulatory decline	Does not capture fatigue, daily functioning, or upper-limb ability
Forced Vital Capacity (FVC)	ALS, neuromuscular respiratory disorders	Objective; correlates with survival	Does not capture swallowing, communication, or nighttime respiratory burden
Spleen Volume Reduction	Myelofibrosis, Gaucher disease	High measurement precision (MRI/CT)	Poor correlation with symptom burden
Timed Function Tests (TFTs)	DMD, ataxias	Reliable motor assessment	Limited real-world relevance; ceiling/floor effects
Biomarkers/ Surrogates	Lysosomal and metabolic diseases	Mechanistic plausibility; supports Accelerated Approval	Often weak correlation to functional outcomes
Patient-Reported Outcomes (PROs)/ Observer-Reported Outcomes (ObsROs)	Pediatric neurodegenerative disease	Capture symptoms directly from patients/caregivers	Few validated tools for ultra-rare diseases

RECOMMENDATION 2
Establish Fit-for-Purpose Tiered Patient-Relevant Endpoint and Biomarker Qualification

Stakeholders should collaborate and develop fit-for-purpose, tiered, patient-relevant endpoint qualification processes to tailor validation requirements to COU. Such tailoring might involve biomarker-to-clinical-outcome bridging studies, or a pathway identifying what is needed to begin initial/exploratory qualification of a biomarker or patient-reported outcome, versus what is needed to support high-stakes endpoints (e.g., primary clinical outcomes with direct patient impact) that will demand stronger, multi-source evidence over time. Elements of such a pathway could include: (a) exploratory/initial validation using historical data, small cohorts, and cross-study triangulation where the evidentiary threshold is feasibility-driven, prioritizing signal-to-noise assessment, data quality, and assay verifiability; (b) interim validation with prospective data collection and pre-specified analysis plans designed to convey not only biological activity but clinical meaningfulness to patients, including identified patient concepts of interest; (c) confirmatory validation with prespecified endpoints, prespecified analytic pipelines, and pre-registered protocols where the evidence is of high-quality and reproducible and demonstrate the endpoint reliably predicts meaningful clinical benefit across populations and contexts. Iterative validation enables rapid progression on endpoint definitions, measurement tools, suitable anchors for establishing thresholds of meaningful change, and data collection methods while maintaining decision-quality risk management.

Discussions about these approaches should: (a) acknowledge rare disease clinical development programs do not always follow standard phases of development (e.g., seamless trials, moving from Phase 1 to confirmatory trials); (b) ensure the value of patients' concept of interest, including the demonstration of incremental improvements over existing standards, is incorporated; and, (c) chart a clear path for understanding how and when post-market surveillance studies will be needed to reduce remaining uncertainty.

A similar approach should also be used to qualify biomarkers where there are stronger mechanistic rationales and human or genetic or translation evidence that links the biomarker to disease progression. A fit-for-purpose evidentiary framework based on COU would evaluate the type of evidence needed to support validation based on whether the biomarker is intended for exploratory decision-making, dose selection, accelerated approval, or full confirmation of benefit. This framework could also include information about how to develop biomarker-to-clinical-outcome bridging studies. Early development may emphasize demonstration of target engagement, biological plausibility, and reproducibility across data sets while later stages could focus on establishing consistent associations between biomarker modulation and meaningful patient outcomes across studies and populations.

Beyond endpoint qualification, these efforts could also communicate information about which statistical methods work best to address specific issues, such as the use of global test methods to overcome small patient populations by aggregating multiple endpoints into a single test to increase statistical power.

CHALLENGE
Translation Gaps Between High-Level Principles and Real-World Operational Needs

Over the past decade, the FDA's PFDD initiative has formalized guidelines for incorporating patient experience data (PED) into drug development and regulatory review. FDA guidance makes clear that patient input can and should inform multiple stages of development, including identification of meaningful treatment benefits, selection of endpoints, and interpretation of trial outcomes. However, FDA also emphasizes that patient relevance alone is insufficient; endpoints must be supported by evidence demonstrating reliability, sensitivity to change, and interpretability within a clearly defined context of use.[5,39. 49,] This framing underpins FDA's broader effort to bridge the gap between what patients have identified as relevant and what regulators can review.

Bridging the gap between patient priorities and regulatory standards requires translating patient-reported symptoms and functional impacts into outcomes that are measurable, interpretable, and suitable for regulatory review. This translation is commonly achieved through structured mapping approaches that link patient-identified concepts of interest to specific COA domains and items—and ultimately to prespecified trial endpoints. FDA's PFDD guidance on selecting, developing, or modifying fit-for-purpose COAs emphasizes the importance of this traceability, noting that regulators must be able to interpret how observed changes in endpoint measures correspond to meaningful clinical benefit for patients.[23] However, in rare diseases this gap is particularly problematic as there is limited availability of validated COAs capable of capturing the full spectrum of patient experience, particularly for heterogeneous, multisystem, and pediatric conditions where symptom expression differs across development stages.[23,24,25] Likewise, there is a lack of validated PROs and ObsROs, despite their importance in capturing symptoms prioritized by patients such as fatigue, cognitive burden, behavioral changes, gastrointestinal difficulties, and day-to-day functional limitations.[50] Thus there is a principle-to-operational gap.

Emerging measurement approaches, including digital health technologies and remote assessments, offer opportunities to align patient experience with regulatory evidence needs.[39,51] For example, wearable sensors and digital endpoints can capture real-world functioning and symptom fluctuation in ways that are less burdensome for patients and more reflective of daily life. Video-based functional assessment of movement and speech also has potential to capture real-world performance in a reproducible, objective manner. The RDEPs signal FDA's willingness to consider these approaches.[52] Additionally, FDA guidance describes the use of qualitative research methods such as in-depth interviews, focus groups, and ethnographic observation to identify

symptoms and functional impacts that patients find most burdensome or meaningful. They recognize these methods as foundational for establishing content validity of COAs, particularly PROs. There are rare disease approvals that illustrate how patient-relevant concepts have been operationalized into regulatory-grade endpoints. In spinal muscular atrophy (SMA), the approval of nusinersen was supported by improvements on validated motor function scales, including the Hammersmith Infant Neurological Examination (HINE) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND). These measures capture functional abilities that patients and caregivers identify as highly meaningful, such as motor control and survival without permanent ventilation, while also meeting regulatory expectations for reliability and interpretability.[53, 54]

The need for endpoints that better bridge the gap between what is meaningful to patients and what is feasible, interpretable, and acceptable to regulators is clear. To achieve this goal there must be greater understanding between regulators and stakeholders about how to operationalize the development and use of patient-relevant endpoints in a rare disease clinical development program.

RECOMMENDATION 3
Advance Methodological Approaches for Patient-relevant Endpoints

Stakeholders should collectively explore, develop, and disseminate methodological approaches that enable the development and utilization of patient-relevant endpoints. These efforts should address operational realities and communicate the scientific principles supporting their use or limitations in specific settings. For example, the 2025 Global Genes RARE Drug Development Symposium included discussion of the item response theory (IRT) psychometric models to detect small changes in patient-reported outcomes and other symptom signatures. The IRT framework enables items to be calibrated on a scale so that each response informs the underlying trait more precisely, even when changes are modest or when baseline severity varies across individuals. A similar framework could be applied to build support for rare disease patient-relevant endpoints, such as how to collect input from patients about what best reflects their experience with sufficient nuance and sensitivity to expose differences at an individual or subpopulation level that might be overlooked by traditional sum scores. This is particularly valuable in rare diseases where patient experiences are heterogeneous and subtle improvements can translate into meaningful daily-life benefits.

Another example discussed during the symposium was the utilization of goal attainment scaling (GAS) to enable individualized outcome assessment and group-level analysis. GAS involves defining personalized goals with patients and caregivers, then rating the degree to which each goal is achieved after an intervention. This approach honors heterogeneity in disease impact and patient priorities, enabling a tailored evaluation of treatment effect that reflects real-world aspirations, such as regaining a specific daily activity or reducing a particular symptom burden.

When aggregated carefully, GAS scores can be standardized to enable comparison across cohorts while preserving the individualized relevance that standard scales may miss. Understanding how and when models such as these could be used would enable more widespread utilization of patient-relevant endpoints.

Additionally, CDER's ARC Program Learning and Education to Advance and Empower Rare Disease Drug Developers (LEADER 3D) could be expanded to include more specific case studies from both CDER and the Center for Biologics Evaluation and Research (CBER), and also hypothetical case studies based on aggregate FDA experience on key issues that are disease specific or agnostic.

RECOMMENDATION 4
Collaboratively Explore and Promote Best Practices for Video- and Sensor-based Functional Assessments

Stakeholders should work together to develop best practices for using video- and sensor-based assessments to record standardized tasks or daily activities and for how to apply validated scoring rubrics for researchers to quantify functional capabilities in contexts that matter to patients, caregivers, and clinicians. These best practices should illustrate how, combined with advances in computer vision and remote assessment platforms, they could offer scalable, longitudinal insights into how a therapy translates to everyday functioning, potentially strengthening the linkage between patient experience and measurable drug benefit. These efforts should also ensure there is a clear path for using AI-powered analysis and machine learning to extract objective movement metrics from unstructured videos, enabling quantitative tracking of motor performance, gait, and dexterity. Discussion of best practices should also acknowledge limitations and variable challenges that need to be addressed, such as standards for wearable or recording conditions (e.g., lighting, camera angle, environment), rating procedures (e.g., blinded raters, predefined scoring rubrics), and quality control (inter-rater reliability checks, artifact rejection, and audit trails) to ensure comparability across sites and over time.

RECOMMENDATION 5
Establish Stakeholder/FDA Consultations for Rare Disease Endpoint Development

The FDA should develop a meeting mechanism for stakeholders leading rare disease endpoint and measurement tool development initiatives, including patient and academic organizations, to convene in the early stages of development. This could include directives about how stakeholders may use current meeting mechanisms to discuss rare diseases endpoint and tool development initiatives and collaborations (e.g., Type C or D meetings). This would enable these organizations to engage FDA and support regulatory acceptance of endpoints and measurement tools.

CHALLENGE

Difficulty Valuing Incremental (Inchstone) Progress

Disease heterogeneity and limited usable natural histories for rare diseases often complicate efforts to determine what constitutes a meaningful improvement.[21] Participants noted that for many rare diseases, especially those with pediatric onset, slowing the trajectory of the disease is the most meaningful treatment effect. But slowing the trajectory may appear as a minor or modest change—an inchstone rather than a treatment milestone. The importance of these inchstones, small but functionally significant gains or stabilizations, are not properly captured in traditional rating scales that have been calibrated for larger effect sizes in more common conditions. The concept of minimal clinically important difference (MCID) is commonly used in non-rare diseases to determine if a therapy provides a patient-relevant benefit.[55,56] FDA's PFDD guidance states that patient experience data should inform the selection of outcomes that are meaningful in patients' daily lives, even when those outcomes represent incremental functional improvements rather than dramatic clinical changes.[23] However, the operational translation of these principles—how small is too small, how much heterogeneity is acceptable, what level of anchor-based evidence is sufficient—remains a source of significant uncertainty for sponsors and clinical development teams.

> *"Patients don't experience diseases in primary and secondary endpoints."*

Participants also discussed how reliance on clinicians to develop protocols may be a factor in continued prioritization of clinical measurements over patient and caregiver-reported measures despite growing commitment to more patient-centric development programs. The FDA Voice of the Patient reports and academic studies have consistently documented the divergence between clinicians' desire for objectively measurable endpoints versus patients' emphasis on symptom burdens and functional independence.[36,57,] Until there is increased cross-stakeholder aligned understandings on how to develop patient-centric endpoints that can be successfully used as a basis for approval or in support of approval, changing these behaviors will remain difficult. This is especially true for endpoints that are measuring MCIDs.

Participants stressed the importance of caregiver-reported outcomes in rare diseases, particularly pediatric and cognitively impaired populations. Participants acknowledged that these measurements need to account for potential 'hope bias' by caregivers, but that caregivers' intimate knowledge of disease trajectory enables them to provide insightful and reliable information on clinical outcomes.[58] Capturing these understandings at an individual level is especially important for rare heterogenous diseases. Additionally, caregivers are important in addressing measurement complexity related to differentiating between a change due to an intervention, such as incontinence, and a child naturally developing skills. A 2025 FDA RISE workshop highlighted the

reliability of caregiver-reported outcomes for rare neuromuscular diseases (consistent >0.85 inter-rater agreement between caregivers and trained clinicians).[39] There was consensus that more training is needed for caregivers to identify the most impactful symptoms prior to treatment and to understand how these symptoms change over time.

RECOMMENDATION 6
Align Evidentiary Thresholds for Slowly Progressive Diseases

Treatments that slow progression without reversing existing disability can provide meaningful patient benefit, but face challenges, especially for rare diseases. Current frameworks emphasize demonstrable functional improvement, while slowed progression (and slower functional decline) may also be meaningful to patients and caregivers. Frameworks that advance regulatory alignment on evidentiary thresholds specific to rare, progressive diseases would be beneficial. In highly prevalent diseases, these approaches often rely on large numbers of patients and a significant amount of time for the condition of the placebo group to worsen to evaluate difference in treatment group. These are two conditions that will not work in small patient populations, many of whom have life threatening or life-limiting diseases.

A framework for progressive rare disease evidentiary thresholds could include:

- **Trajectory Analysis Standards:** A robust framework for slowly progressive rare diseases should shift the emphasis from binary "improved/not improved" dichotomies to changes in the disease trajectory over time. Trajectory analysis compares the slope and shape of functional decline or biomarker progression between treated and control groups, capturing how the rate of decline is altered, even if absolute function at a given time point remains below normal. This aligns with patient experiences where slowing progression preserves independence and quality of life longer than transient improvements.
- **Progression-slope Endpoints:** Progression-slope endpoints quantify how quickly a disease advances, offering a sensitive and clinically meaningful alternative when fixed-timepoint endpoints fail to capture slow progression. By focusing on the rate of decline (or growth) in function, imaging biomarkers, or composite scales, these endpoints can detect treatment effects that accumulate gradually and may be missed by traditional endpoints that compare participants at a single timepoint.
- **Delayed Decline Thresholds:** Delayed decline thresholds aim to translate slowing of progression into tangible, patient-centered milestones, such as time to loss of driving eligibility, assistive device use, or need for formal care. This approach requires defining what constitutes a meaningful delay for specific diseases and care contexts, informed by patient preference studies, caregiver input, and health economic considerations.
- **Rare Disease Patient Population Analyses Considerations:** These standards, endpoints, and thresholds should encourage totality of evidence approaches and consider the small patient populations of rare diseases, with appropriate timelines for progressive rare diseases.

RECOMMENDATION 7
Develop and Implement Training Programs on Data Collection for Patients and Caregivers

Consistent training programs for organizations and individuals responsible for the collection and reporting of patient perspective data, including caregiver data, would improve data reliability and stakeholder trust in rare disease research. Programs should specify competencies in outcome reporting, ethical data handling, and effective communication with clinicians and researchers. Biopharmaceutical companies, in collaboration with medical researchers and patient organizations, should develop and disseminate these training programs. Additionally, biopharmaceutical companies could provide training programs to patient organizations, which they could then use to train patients and caregivers charged with collecting and reporting data in clinical trials.

CHALLENGE
Endpoint Triangulation and Composite Endpoint Uncertainty

In rare diseases where no single measure can adequately capture treatment benefit, FDA and academic literature increasingly recognize the value of both endpoint triangulation and use of composite endpoints.

Endpoint triangulation involves the use of multiple types of evidence to confirm a therapeutic effect or clinical benefit such as combining quantitative data (e.g., lab results) with qualitative data (e.g., patient interviews) or integrating results from randomized trials with RWE to obtain a more holistic view of the treatment's impact. Endpoint triangulation is also used to describe how a primary endpoint (e.g., tumor shrinkage) may be 'triangulated' by secondary endpoints (e.g., reduced fatigue) to demonstrate clinical benefits. Triangulation can reduce uncertainty and strengthen interpretability in small, heterogeneous populations by allowing converging lines of evidence to support conclusions about clinical benefit.[59]

Roundtable participants also discussed the potential benefit of using composite endpoints to capture multidimensional treatment benefit in heterogeneous rare disease populations. Well-designed composite endpoints can increase statistical power, reduce required sample sizes, and accelerate trial completion by combining multiple clinically relevant outcomes (e.g., survival, hospitalizations, symptoms) into a single measure.[60,61] Additionally, single clinical outcomes with substantial patient impact are often measured discretely in multiple domains of severity, frequency, and intensity. Each of these domains can vary within patients but with equivalent clinical impact. Combining these domains into a single endpoint would enhance the ability to assess meaningful outcomes. Although FDA guidance on composite endpoints has largely focused on cardiovascular outcomes, FDA has accepted composite endpoints in rare lysosomal storage disorders and neuromuscular diseases (e.g., treatment with Miplyffa (arimoclomol)).[62,63,64] But the interpretation

of aggregate scores is an area where methodological and regulatory uncertainty remain, limiting development and adoption.

The FDA's RDEP acknowledges the need for flexibility in evidentiary approaches while maintaining methodological rigor, particularly when traditional randomized trial paradigms are infeasible.[38] Participants recommended additional work to better enable utilization of endpoint triangulation and composite endpoints in rare disease clinical development.

Imagine an environment where rare data is used to its maximum value…

WHAT IF: Every rare disease patient organization had access to patient and caregiver data collection training programs they could use to ensure their communities consistently collect and report high quality data. Imagine biopharmaceutical, government, and charitable funders working together to develop and deploy core training modules to patient organizations. These training modules could be designed for individual disease or clinical development data collection efforts and for disease-agnostic data collection efforts. They could include training for data collection relating to registries, natural history studies, and clinical trial patient and caregiver reported outcomes. These efforts could 1) Enable training to come from organizations that are trusted by patient and caregiver communities and who are engaged with those communities on a regular basis; 2) Ensure data collected is high quality and regulatorily usable; and 3) Better enable consistent data collection efforts that could support building or combining data platforms. Such widespread training could significantly streamline and optimize rare disease data collection and use. Further, these efforts would lead to improved understandings about the impact of diseases and enable the development of more meaningful endpoints.

RECOMMENDATION 8
Enable Use of Endpoint Triangulation and Composite Endpoints

Stakeholders should collaborate and develop alignment on how to perform endpoint triangulation of multiple endpoints with enough sensitivity to measure relevance and meaningfulness in rare disease populations. Similarly, alignment on how composites can capture multifaceted disease trajectories– even as individual components evolve during a trial– is needed. These efforts should include illustrations about how a well-designed composite can yield a usable, interpretable primary or key secondary endpoint at trial completion, even when therapeutic effects may manifest variably across domains and time. Advancing these areas in rare diseases will require methodological guidelines and consensus–addressing triangulation approaches, sensitivity analyses, and regulatory acceptability.

RECOMMENDATION 9
Expand FDA Grants to Advance Composite Endpoint Methodological Approaches

Expand use of OOPD grants to address methodological gaps that impede utilization and acceptance of composite endpoints in rare diseases.

CHALLENGE
Unclear Pathways for Disease-Agnostic Endpoint and Measurement Tool Development

One of the most significant obstacles facing rare disease communities is the lack of robust infrastructure for developing clinical endpoints outside of specific product development programs. When patient organizations or academic researchers pursue endpoint development independently, the work is often referred to as product-agnostic or disease-agnostic and there are limited mechanisms for engaging with the FDA or pursuing full regulatory qualification. Current regulatory engagement models are inherently product-centric, meaning that without a sponsor-driven meeting to initiate dialogue, there is no clear pathway for early and ongoing collaboration with regulators. This creates a structural gap for the development of disease-agnostic endpoints and tools for symptoms that span multiple diseases (e.g., mobility, cognition, fatigue).

While some promising examples of disease-agnostic work exist—such as the Observer-Reported Communication Ability (ORCA) measure, originally developed for Angelman syndrome and now expanding to additional disorders through an FDA grant—these efforts remain limited in scale. Advocates have called for dramatically increasing the reach, scalability, and speed of such initiatives. Existing infrastructure, such as the FDA's Drug Development Tools Qualification Program, the Critical Path Institute's Rare Disease COA Consortium, and the EMA's Innovation Task Force, provides some formal pathways, but uptake has been modest and the evidence generation required for qualification often exceeds the resources available to patient organizations and academic groups.

Advancing disease-agnostic approaches will require new funding models, stronger coordination mechanisms, and a reimagining of how regulators interact with non-industry stakeholders. Patient advocacy organizations are often best positioned to design and oversee disease-agnostic data collection efforts, yet they often lack financial backing, institutional support, and methodological expertise to do so at scale and do not have clear pathways to engage with FDA to discuss the development of disease-agnostic measurement tools. The FDA's Rare Disease Hub 2026 Strategic Agenda acknowledges the need to explore new engagement mechanisms for stakeholders working outside of traditional product applications, and operationalizing this commitment will be critical to closing the current infrastructure gaps. Participants flagged that incentives for pre-competitive collaborations may be needed for these efforts to be more widespread and impactful.

RECOMMENDATION 10
Support Development and Use of Disease-Agnostic Endpoints and Tools

The endpoint and evidentiary threshold recommendations discussed in previous sections of this document should include information that would advance the development of disease-agnostic endpoints and tools for common human functional evaluations, such as speech, vision, ambulation. The ORCA measure provides an excellent roadmap for developing disease-agnostic tools. It is important that discussions around disease-agnostic tools and approaches continue to reflect the value of MCIDs and how to ensure their benefit is captured. Similarly, the FDA endpoint meeting consultation recommendation should also be made available for stakeholders working on disease-agnostic approaches and consultations.

Lastly, FDA should convene stakeholders to examine common functional rare disease domains (e.g., communication, mobility, fatigue, independence) and identify topics that will enable detailed and substantive discussions that support the development of these types of endpoints and tools. These workshops should emphasize opportunities and considerations for developing specific disease-agnostic endpoints.

RECOMMENDATION 11
Establish Incentives for Large-Scale, Pre-Competitive Disease-Agnostic Data Collaboration

Incentivizing pre-competitive collaborations to build disease-agnostic databases and tools could play a pivotal role in addressing the fragmented data landscape that characterizes many rare diseases. Such efforts would enable data from millions of patients with diverse rare diseases to be leveraged to unlock new understandings about evaluating common physiological conditions and support improved geno- and phenotype analyses, which are foundational to drug discovery and diagnoses. While there are examples of these types of collaborations, efforts remain siloed. Support for these collaborations requires significant funding to build and maintain infrastructures that support large-scale data collection and analyses; develop and implement training; ensure quality of data and processes; and optimize data access and reusability. Additionally, these platforms should be AI-enabled and have strong cybersecurity protections. Developing incentives for biopharmaceutical companies to share data and make these investments would greatly improve scaling and optimize impact of these collaborations.

Imagine an environment where analyses of rare disease data platforms are maximally optimized…

WHAT IF: **Large-scale data platforms for natural history studies for multiple rare diseases were the norm.** Combining current platforms or creating cloud and AI technologies would enable better interrogations and analyses across differing platforms. Incentivizing funding for such efforts could significantly advance concepts such as developing disease-agnostic tools that work across multiple rare diseases (e.g., fatigue, ambulation, communication). This would help decrease duplicative efforts, reduce patient burden, help support the consistent collection of high-quality data and advance shared understandings about rare diseases and what matters most to patients.

RECOMMENDATION 12
Create Function-Based, Domain-Driven Endpoint Libraries

A domain-based endpoint library developed by the government and available to the public that organizes endpoints by functions, such as communication, mobility, and self-care, rather than tying measures to individual diseases, would be beneficial. By cataloging and harmonizing endpoints within each clinical domain, researchers could share measurement strategies, validation data, and interpretability frameworks across multiple rare conditions, enabling cross-disease learning and more efficient regulatory qualification processes.

TOPIC 2

Optimizing Patient Perspective and Natural History Data Collection and Use

CHALLENGE

Fragmented and Burdensome Data Landscape

Natural history studies are essential for rare disease clinical development, but the information is often limited and frequently fails to meet regulatory standards. This is particularly true for older studies that were not intended to support regulatory decision-making. RWE from registries and natural histories can also be used to characterize diseases, to better understand patient experiences, and serve as external control arms when placebo or active comparator arms are not ethical or feasible. By aggregating longitudinal natural history data and well-curated registry information, researchers can illuminate disease trajectories, clarify endpoint concepts, and inform trial design. However, this data may mature on a timeline that is longer than clinical development programs, and the regulatory path for such data remains uncertain or limited, with acceptance criteria not yet clearly articulated across agencies and programs. For example, the FDA Guidance on Externally Controlled Trials states that, "Scenarios that would not be suitable for externally controlled trials include when the natural history of the disease of interest is not understood sufficiently or when the disease course is considered well-understood but is variable," a common situation in rare diseases.[65] Additionally, participants discussed how the current natural history environment is highly siloed, of varying quality, and burdensome to patients. They emphasized that because of the small patient populations, many patients are being asked to participate in myriad natural history studies and registries. The participants also discussed the issue of varying quality in data collection efforts and the need for more consistent training across academics, patient organizations, and medical researchers to better ensure natural histories can be used to support regulatory decision-making. One of the key findings from the 2024 FDA-Reagan Udall Foundation workshop "Natural History Studies and Registries in the Development of Rare Disease Treatments" was that inconsistent case definitions, variable data collection protocols, and limited standardization of outcome measures have compromised regulatory utility of many natural history studies.[66] Participants noted that while there has been significant investment in the Critical Path Institute's Rare Disease Cures Accelerator Data and Analytics Platform (RDCA-DAP) to promote the sharing of patient-level data and to encourage the standardization of new data collection, its impact on improving the availability of regulatory-relevant data remains limited.

Further, patients who contribute data to registries, natural histories, and trials have consistently stated they want to be informed about how their data is being used and how those contributions are improving medical care for rare disease patients and their families. Participants indicated that to better inform patients about how their data is used and to maximize the use of their data,

reforms to data consent and reuse are needed. Trial sponsors have stated that to improve ability to use data for multiple research initiatives or for regulators to use data for their own research purposes, improved understandings about how to operationalize data consent practices that hold up under legal and regulatory scrutiny are needed.

> *"Patients are spending their time, their money, and their lives participating—we owe them clarity on how that data is used."*

Systematic data sharing initiatives, such as centralized, precompetitive data platforms with standardized data models, controlled-access governance, and reproducible research workflows, have been shown to accelerate discovery, validation, and cross-trial insights in oncology and offer a transferable template for rare diseases.[67,68] These approaches could create a less fragmented data landscape in rare diseases and significantly reduce patient burdens. Participants noted that incentives for these types of collaborations will be critical to their success.

Lastly, participants discussed how natural histories can be used to characterize diseases, to better understand patient experiences, and serve as external control arms when placebo or active comparator arms are not ethical or feasible. However, they noted clarity about regulatory expectation for each of these uses is needed for this data to reach their full potential.

> *"Every single patient's data counts."*

RECOMMENDATION 13
Advance Best Practices for Responsible Rare Disease Data Sharing

Stakeholders should work together to develop best practices for responsible data sharing that would optimize data collection and clinical research for rare diseases.

Two examples could serve as the basis for developing and promoting widespread rare disease data sharing.

- Project Data Sphere (PDS) is a multiplatform, precompetitive data-sharing initiative that aggregates de-identified clinical trial data from multiple oncology sponsors and makes it accessible to researchers for secondary analyses, meta-analyses, and hypothesis testing.[69,70] It emphasizes standardized data models, governed access, and reproducible research workflows to maximize the value of trial data while safeguarding patient privacy and sponsor interests. By providing a centralized, well-governed environment for data harmonization, query-able datasets, and transparent usage tracking, PDS demonstrates how systematic data sharing can accelerate discovery, validation, and cross-trial insights in oncology, including opportunities to identify rare subtypes, comparative effectiveness, and biomarker associations across large populations.

- The Global Alliance for Genomics and Health developed data sharing standards and frameworks for the responsible sharing of genomic and related health data.[71] They have developed interoperability policies, consent templates, and data access governance that supports broad data sharing for research while maintaining robust privacy protections and participant trust.

It will also be important that these efforts work to ensure that data sharing platforms are AI-enabled and have strong cybersecurity measures. Elements of best practices could include:

- **Broad Data Sharing Permissions** (e.g., broad informed consent): Empirical work and policy analysis in rare disease research emphasize that consent should explicitly authorize future use of de-identified data for ongoing and future research, regulatory submissions, and public repositories to maximize data reuse while preserving participant privacy.
- **Distinction Between Treatment Discontinuation and Study Withdrawal:** Clear differentiation between treatment discontinuation and study withdrawal in consent language that supports continued data collection critical for evaluating real-world effectiveness, safety signals, and natural history—even when a participant stops receiving the experimental intervention— could be beneficial.
- **FAIR Data Principles:** FAIR data principles provide internationally recognized standards for data stewardship.[72] These principles emphasize participants' data contributions to be Findable, Accessible, Interoperable, and Reusable (FAIR)—fostering data sharing for rare diseases while supporting reproducibility and secondary analyses—should be integrated into best practices.
- **Standardized Phenotype Ontologies**: Adopting established phenotype and laboratory data ontologies (e.g., Human Phenotype Ontology) with explicit guidance on appropriate granularity is essential for rare disease data interoperability. Standard ontologies enable precise phenotyping, cross-study comparisons, and reliable data linking across clinical records, registries, and biobanks.
- **Data Quality Frameworks:** A robust data quality framework should define minimum standards for data completeness, accuracy, consistency, and timeliness, along with explicit validation procedures and temporal requirements.

RECOMMENDATION 14
Create Tiered Approaches for Natural History and Registry Data Acceptability

Stakeholders should convene to co-create regulatory alignment on tiered natural history and registry data acceptability approaches that map data quality, provenance, and analytic methods to regulatory uses. These efforts should also aim to translate practical RWE collection into standardized expectations, reduce interpretive ambiguity, and accelerate thoughtful integration of external data into decision-making processes.

A hierarchical RWE quality approach could provide a common language for evaluating registry and natural history data across regulatory contexts. For example, Tier 1 could focus on disease characterization and endpoint concept identification, requiring basic data quality and consistent case definitions. Tier 2 could focus on natural history modeling for trial design and enrollment estimation, emphasizing longitudinal follow-up and standardized outcome assessments. Tier 3 could focus on external control arms for single-arm trials in highly progressive diseases, demanding contemporaneous data, detailed baseline characteristics, and outcomes measured identically and at a comparable "time zero" to interventional trials. Lastly, Tier 4 could focus on exceptional circumstances, necessitating prospective designs with regulatory-grade data quality.

These efforts should also work to 1) advance understandings about how best to approach the collection of natural history study concurrently with early-stage clinical trials and 2) how to remove current barriers to using external control arms when randomized controls are ethically or practically infeasible.

RECOMMENDATION 15
Clarify Evidentiary Requirements for Utilizing Legacy Registry Data

Substantial rare disease data exist in registries and natural history studies collected before regulatory use was contemplated; yet, unclear standards prevent effective utilization of the content. Stakeholders should work together to clarify evidentiary requirements for the utilization of legacy registry data, evaluating such requirements through the context of specific diseases to accommodate variable data needs. Elements of these efforts could include:

- **Minimum Salvageability Criteria:** Define minimum salvageability criteria for legacy registry data that clarifies when such data can meaningfully support regulatory decisions despite imperfect prospective design.
- **Statistical Methods for Legacy Data:** Guidance on statistical methods for legacy data that discusses how to address quality limitations, missingness, and temporal discordance between data collection and trial timing.
- **Supplemental Evidence Requirements:** Guidance on how supplemental evidence could bolster evidentiary credibility, such as comparative analyses with contemporary registries or natural history datasets, and triangulation using related endpoints or registries with overlapping populations.
- **Contemporaneity Standards:** Clarifying contemporaneity standards, including defining acceptable temporal windows between registry data collection and the initiation or conduct of clinical trials.
- **Evaluation of Representativeness:** Clarifying how, or whether, natural history study data can be utilized if the data is more limited than the population being evaluated in a clinical trial (i.e., natural history study explores a specific genotype but trial population is broader than patients with that specific genotype).

TOPIC 3

Advancing Shared Understandings of Evidentiary Expectations and Regulatory Requirements

CHALLENGE:

Lack of Clarity on Scientific Principles Driving Different Evidentiary Expectations and Regulatory Requirements

Sponsors developing therapies with common mechanisms across multiple rare diseases stated they often face differing regulatory expectations depending on the FDA division evaluating their application. And while different patient populations may have nuances that compel such disparate treatment, sponsors expressed a lack of shared understanding of the scientific basis for differing requirements. The FDA RISE workshop held in September 2025 included documented experiences of sponsors receiving divergent advice across divisions (e.g., division A accepted external control arms for a rare neuromuscular indication while division B reviewing a related disease with similar rarity required randomized controlled trials despite feasibility constraints.)[39]

Participants engaged in a robust discussion about the need for regulatory flexibility and the desire to have that flexibility applied consistently. Participants simultaneously acknowledged that flexibility is inconsistent with a standard approach. However, there is a need to advance understanding between sponsors and regulators about the scientific principles being used to determine what evidence is needed to support the use of regulatory flexibility within and across different rare diseases. During the 2024 RISE workshop "Defining Adequate and Well-Controlled Investigations in Rare Diseases," sponsors discussed the lack of operational clarity about when and how flexibility will be allowed. FDA's RDEP process is intended to help clarify what flexibility means and acknowledges that its application is context-dependent (e.g., rarity, available therapies). Further clarity is needed.

The FDA has taken steps to better align cross-center and cross-division rare disease regulatory decision-making. The FDA has a Rare Disease Consult Service, mandated by ARC, to support rare disease reviews across divisions. The FDA Rare Disease Innovation Hub also launched the Rare Disease Policy and Portfolio Council, a senior level forum to promote cross-center dialogue on challenging and complex rare disease development program issues.

The FDA has also consistently stated that sponsors should engage with the agency early and often with the goal of identifying and resolving as many issues as possible early in the clinical development process. How to effectively utilize the current FDA-sponsor meeting structure to achieve those goals remains somewhat unclear. For example, participants discussed difficulty in sharing data accumulated for molecules being studied across multiple indications with the FDA in

a more general setting to discuss evidentiary expectations that should transcend across reviews. It was pointed out that sponsors can request cross-divisional meetings—a process that was not known to many in the meeting. For those participants who have requested such a meeting, they observed that such meetings are not always granted.

> *"Time and money are not saved at the end, they are saved in the beginning."*

RECOMMENDATION 16
Promote Shared Understandings of Scientific Principles Supporting Flexible Evidentiary Strategies

Stakeholders should work together to develop and publish more documents about approved and failed rare disease applications with explicit notes on how evidentiary gaps were addressed (successfully or unsuccessfully), while also protecting proprietary information. Such publications should present the clinical rationale, the chosen endpoint suite, and the supplementary data that compensated for conventional gaps (e.g., reliance on natural history data, historical controls, mechanism-based biomarkers, patient-reported outcomes, cross-disease analogues). For example, a high-quality case study would clearly identify what would traditionally be required (i.e., the baseline reference evidentiary standard) and what was accepted in practice (i.e., the flexible approach), including the regulatory rationale and the conditions attached to approval (i.e., post-marketing commitments, risk mitigation strategies, data-generation plans) or reasons for denying approval. The value of these types of case studies and communications lies in making transparent the conditions regulators are willing to accept when there is solid reasoning about disease biology, patient impact, and the plausibility that observed effects are attributable to the therapy rather than confounding factors. An effective set of illustrated cases should also discuss what compensations were accepted or rejected for gaps in traditional evidence (e.g., reliance on disease natural history data to contextualize effect sizes, cross-disease endpoint translatability, extended follow-up to assess durability) and would note any recurring themes (e.g., primacy of clinically meaningful outcomes, credibility of biomarkers as surrogate endpoints, role of patient input in endpoint relevance). These types of communications could serve both as training references for sponsors and as evidence of regulatory practice patterns that can inform future guidelines on flexible evidentiary strategies. These documents should be published on a regular basis by both regulators and sponsors. Regulators could help prioritize communication and case study development by indicating areas where patterns have begun to emerge and where case studies would be beneficial.

RECOMMENDATION 17
Enable Early Identification and Resolution of Issues for Novel Endpoints and Trial Designs

While there are many meeting mechanisms available to sponsors, it is not always clear which should be used to have in-depth conversations about novel endpoints and trial designs, including mechanistic issues that span multiple diseases. It can also be unclear how best to prepare for those meetings to ensure both regulators and sponsors are focused on the issues that must be resolved (e.g., recommended topics and points to consider in briefing materials for Type C meeting[73]). Lastly, clarity is welcome on the role of informal communications, such as phone calls, in obtaining timely responses to simple questions.

To implement this recommendation, FDA should hold a public meeting to understand what clarifications are needed and publish an FAQ on best meeting practices for rare disease clinical development programs.

CHALLENGE
Successfully Incorporating Learnings Generated During a Clinical Trial

Another challenge in rare diseases is that unanticipated discoveries may not fit pre-specified adaptation rules. Additionally, because many of these diseases are heterogeneous, population effects may obscure clinically meaningful responses in subgroups. Further, caregivers may observe and report unexpected benefits of treatments that need to be considered. Exploratory analyses, including post hoc or subgroup analyses, generally cannot serve as the primary basis for establishing substantial evidence of effectiveness because they lack prospective specification and control of Type I error. However, in rare diseases where traditional trial designs may be infeasible, FDA may consider exploratory findings as part of the totality of evidence when they are supported by biological plausibility, consistency across multiple data sources, and a scientifically sound understanding of disease pathophysiology.

The 2025 RISE Workshop on controls in small and diminishing rare disease populations discussed the concept of a prospective exploratory framework, in which sponsors would pre-specify the full universe of endpoints to be collected, delineate planned exploratory analyses in advance, and define statistical thresholds clarifying when findings would be considered hypothesis-generating versus potentially supportive of regulatory decision-making. This approach was described as a mechanism to enable broader data collection and learning in very small populations while preserving transparency and inferential discipline.

Bayesian designs formally incorporate prior information (e.g., historical data, natural history, results from related diseases) to improve feasibility. Adaptive designs, while operationally challenging, allow flexible interim adaptations and maintain valid inference. These trial designs can be used to explicitly balance learning from accruing data while maintaining the scientific standards needed for

credible inference but may require decentralized trial elements and central statistical monitoring. This is an especially important advantage in rare diseases, where trials may enroll a substantial proportion of all patients and each participant's data is uniquely valuable.

There are additional endpoint interpretation and comparator arm relevance complications when the standard of care evolves over the course of a clinical trial. Platform trials are perpetual, adaptive master protocols that allow new treatment arms to be added, and inferior arms dropped over time, under a unified protocol. In practice, a rare disease platform might continuously enroll patients in new experimental therapies as they emerge, always comparing active arms to a shared contemporaneous control (or external data). Response-adaptive randomization (RAR) reallocates patients during a trial to favor treatments showing greater benefit on interim analysis. This can be ethically attractive in severe, rapidly progressive diseases, especially for pediatric populations. Effectively, RAR limits patient exposure to ineffective therapies, which is especially important when each patient's outcome is life-altering. Adoption of RAR has so far been limited outside exploratory settings, but interest is growing. The benefits and limitations of these designs are discussed in FDA's 2019 guidance, Adaptive Design Clinical Trials for Drugs and Biologics.[74]

The FDA 2025 RISE Workshop discussed how the increasing number of rare disease approvals is making untreated natural history studies obsolete and placebo control arms more ethically complex. The Workshop noted that additional cross-stakeholder alignment on how to design trials and utilize real-world evidence and natural history data in these circumstances is needed. Participants discussed the overall need to continue to advance regulatory understandings about how to prospectively design studies that can adapt to new knowledge that may be gained during a trial.

The increase in the number of approvals has also ushered in second-in-class, third-in-class, and combination treatments. In these cases, recommendations for treatments may include the use of multiple approved therapies. Participants expressed a need for regulatory clarity on topics such as evidentiary requirements for second- and third-in-class treatments when the treatment paradigm and disease trajectory have been altered, standards for demonstrating incremental benefit beyond existing standard of care, and how to update registries.

RECOMMENDATION 18
Enable Rare Disease Clinical Trials to Learn and Adapt More Effectively

Stakeholders should work to develop best practices for responding to unexpected findings that fall outside the original pre-specified rules established for a clinical trial, such as how best to design exploratory studies that can be used to support regulatory decision making and to develop protocols with prespecified flexibilities. Communications that illustrate successful or failed approaches to addressing specific clinical trial design challenges such as patient scarcity, clinical heterogeneity, and evolving standard of care would be beneficial.

RECOMMENDATION 19
Define Evidentiary Thresholds for Rare Disease Second- and Third-Line Treatments

Stakeholders should collaborate to advance shared understandings of evidentiary thresholds requirements and expectations for second- and third-line treatments. These efforts should advance alignment on the following topics:

- **Evidentiary Thresholds for Incremental Benefits**: Evidentiary requirements for second- and third-in-class treatments when initial therapies have altered disease trajectory;
- **Add-On Therapy Trial Designs**: Methodological standards for demonstrating incremental benefit beyond existing standard of care; and
- **Continuous Natural History Updates:** How to enable continuous registry updates that provide contemporary comparisons.

TOPIC 4

Improving Cross-Stakeholder Knowledge Management

CHALLENGE

Difficulty Translating Siloed Knowledge Management Improvements into Broader Public Benefit

FDA accumulates extensive knowledge from reviewing multiple rare disease applications. But there are limitations to what the FDA can share with stakeholders, either during a review or publicly, as the agency is required to keep commercial and proprietary information confidential.[75] Participants were interested in better understanding how this growing body of knowledge and newly established cross-center and cross-division collaborations are advancing alignment on regulatory decision-making practices in rare diseases. Further, there was great interest in how these learnings could be shared externally to support better decision making by sponsors. The FDA is now publishing Complete Response Letters (CRLs) for both approved and unapproved drugs on a publicly available website to provide detailed information about the FDA's review process and deficiencies identified in applications to help drug developers avoid common missteps.[76]

Sponsors and patient organizations are continually accumulating knowledge, but the knowledge is insufficiently shared. Participants agreed it would be beneficial if all stakeholders prioritized publication of both successful and failed clinical development programs. They also stated that stakeholders should publish more case studies illustrating successful and failed approaches to specific elements of a clinical trial (e.g., evidence to support use of endpoint, statistical methodologies, trial designs). It was noted that publication bias favoring positive results could be limiting access to knowledge gained from failed programs and approaches.

RECOMMENDATION 20
Build a Cross-Stakeholder, AI-enabled, Rare Disease Knowledge Management System

Systematic knowledge sharing, both within regulatory agencies and with external stakeholders, is essential to accelerate drug development and patient access. FDA has taken significant steps to improve its rare disease internal knowledge management systems, including external information such as scientific publications and internal information such as application and review details. Creating a government housed, cross-stakeholder, and AI-enabled knowledge management system would help medical researchers, sponsors of clinical development, and regulators better identify patterns and improve decision-making. Key features could include the following:

- **Endpoint Performance Database:** A database that includes all endpoints used in rare disease trials—both successful and unsuccessful—with information on measurement properties, implementation challenges, and regulatory outcomes.
- **Regulatory Precedent Repository:** Capture patterns in regulatory decision-making while preserving commercial confidentiality.
- **Natural History Data Standards Repository:** Define minimum quality standards for natural history studies intended to support regulatory decisions.
- **Domain-Based Measurement Library:** Organize endpoints by clinical domain (e.g., communication, mobility, independence) rather than disease, enabling cross-disease learning.
- **Trial Feasibility Data:** Enrollment rates by diseases, reasons for screen failures, and protocol amendment histories.

Development of a government-housed (or government-adjacent) knowledge management system will require public and private funding mechanisms and broad stakeholder collaborations that include AI, cybersecurity, and machine-learning expertise.

CONCLUSION

There has been significant progress in the development of treatments for rare diseases, but much more is needed. FDA has done significant work to improve the regulatory environment for rare disease product development, evident by the many initiatives and activities it has implemented. The complex scientific, clinical, and operational aspects of rare disease drug development require a dynamic and collaborative regulatory environment. This Roundtable was convened to ensure that the value and importance of using patient-relevant endpoints in rare disease clinical development programs is understood and enabled. The actionable recommendations put forward from this meeting are an urgent call to action to better leverage research efforts, create more iterative and operationally helpful information, and usher in an environment that is more reflective of what matters most to patients.

Imagine a more patient-centric rare disease clinical development ecosystem...

WHAT IF we had an ecosystem where:

- Fit-for-purpose, patient-relevant endpoint and biomarker qualifications are routinely provided;
- There is a publicly available, domain-driven endpoint library so no sponsor, patient organization, or academic researcher must build novel endpoints from scratch;
- Composite and triangulated endpoints are routinely accepted as primary or key secondary endpoints in rare disease clinical trials;
- There are evidentiary thresholds explicitly designed for slowly progressive diseases - where slowing a child's decline, preserving a daily function, or delaying the need for assistive care was recognized as a meaningful treatment effect; and
- The use of disease agnostic endpoints and tools are common.

These changes could: (1) break the precedent paradox and support the development and utilization of endpoints meaningful to patients; and (2) reduce per-program costs and timeline burdens of endpoint development by creating shared infrastructure that benefits the entire rare disease community.

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APPENDIX A

Table 1. Topics, Challenges, and Recommendations

Developing Regulatorily-Acceptable Patient-Relevant Endpoints				
Recommendations	**Challenges**	**Next Steps***	**Product**	**Stakeholders**
1. Enable Mutual Recognition of Endpoint Qualifications	• Misaligned Validation and Qualification Timelines with Patient Need • The Precedent Paradox That Limits Acceptance of Novel Approaches	FDA and key regulatory agencies collaborate with sponsors to develop processes for mutual recognition agreements	Mutual recognition agreements, data sharing platform that enables collaborative work between multi-regional regulatory authorities and sponsors	FDA, regulated industry, EMA, other key regulatory authorities
2. Establish Fit-for-Purpose Tiered Pathways for Patient-Relevant Endpoint and Biomarker Qualification	• The Precedent Paradox • Translation Gaps Between High-Level Principles and Real-World Operational Needs • Lack of Clarity on Pathways for Developing and Using Disease-Agnostic Endpoints and Measurement Tools	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Frameworks published by FDA	FDA, ICH, regulated industry, patient organizations, medical researchers
3. Advance Methodological Approaches for Patient Relevant Endpoints	• The Precedent Paradox • Translation Gaps Between High-Level Principles and Real-World Operational Needs • Difficulty Valuing Incremental (Inchstone) Progress • Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Framework (and potential guidance) published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, regulated industry, patient organizations (specifically including patients and caregivers), medical researchers, clinical research organizations
4. Collaboratively Explore and Promote Best Practices for Video- and Sensor-based Functional Assessments	• Translation Gaps Between High-Level Principles and Real-World Operational Needs	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Guidance published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, regulated industry, patient organizations, clinical research organizations, medical researchers
5. Establish Stakeholder/FDA Consultations for Rare Disease Endpoint Development	• Misaligned Validation and Qualification Timelines with Patient Need • The Precedent Paradox • Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development	FDA public meeting with public speakers and public comment period (addressing targeted topics and enabling discussion to yield substantive solutions)	FDA publication of new meeting mechanism and/or FAQ on best practices for scheduling and preparing for a dedicated rare disease endpoint meeting	FDA, regulated industry, patient organizations
6. Align Evidentiary Thresholds for Slowly Progressive Diseases	• The Precedent Paradox • Translation Gaps Between Principles and Operational Realities • Difficulty Valuing Incremental (Inchstone) Progress • Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Framework published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, ICH, regulated industry, patient organizations, medical researchers

7. Develop and Implement Training Programs on Data Collection for Patients and Caregivers	• Translation Gaps Between Principles and Operational Realities	Training program development for patient experience data reporting and collection	Training program deployed to clinical sites and to patient organization; patient organization to deploy training programs to patients and caregivers	Regulated industry, medical researchers, patient organizations, contract research organizations
8. Enable Use of Endpoint Triangulation and Composite Endpoints	• The Precedent Paradox • Translation Gaps Between Principles and Operational Realities • Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development • Endpoint Triangulation and Composite Endpoint Uncertainty	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Framework published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, ICH, regulated industry, patient organizations, medical researchers
9. Expand FDA Grants to Advance Composite Endpoint Methodological Approaches	• The Precedent Paradox • Endpoint Triangulation and Composite Endpoint Uncertainty	FDA to expand/prioritize funding	Grants provided; publication of funded studies	FDA
10. Support Development and Use of Disease-Agnostic Endpoints and Tools	• Difficulty Valuing Incremental (Inchstone) Progress • Unclear Pathways for Disease-Agnostic Endpoint and Measurement Tool Development	**Stakeholder workshop(s)** FDA public meeting with public speakers and public comment period (addressing targeted topics and enabling discussion to yield substantive solutions)	Inclusion in frameworks, case studies and peer reviewed publication for recommendations to: enable use of endpoint triangulation and composite endpoints; develop alignment on evidentiary thresholds for slowly progressive diseases; collectively explore, develop and disseminate methodological approaches for patient relevant endpoints; advance regulatory understandings for use of patient experience data to support endpoint acceptance; develop and enable fit-for-purpose tiered patient-relevant endpoint qualification; and establish stakeholder–FDA rare disease endpoint consultations	FDA, ICH, regulated industry, patient organizations, medical researchers
11. Establish Incentives for Large-Scale, Pre-Competitive Disease-Agnostic Data Collaboration	• The Precedent Paradox • Translation Gaps Between Principles and Operational Realities • Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development • Fragmented and Burdensome Data Landscape	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Statutory and regulatory incentive proposals	FDA, regulated industry, medical researchers, patient organizations, data scientists
12. Create Function-Based, Domain-Driven Endpoint Libraries	• Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development	FDA public meeting with public speakers and public comment period (addressing targeted topics and enabling discussion to yield substantive solutions)	A publicly available, government housed or government-adjacent, domain-based endpoint library	FDA, regulated industry, medical researchers, patient organizations

Optimizing Patient Perspective and Natural History Data Collection and Use

Recommendations	Challenges	Next Steps*	Product	Stakeholders
13. Advance Best Practices for Responsible Rare Disease Data Sharing	• The Precedent Paradox • Translation Gaps Between Principles and Operational Realities • Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development • Fragmented and Burdensome Data Landscape	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Framework published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, EMA/global regulators, regulated industry, medical researchers, patient organizations, clinical research organizations, privacy lawyers, data/AI companies
14. Create Tiered Approaches for Natural History and Registry Data Acceptability	• The Precedent Paradox • Translation Gaps Between Principles and Operational Realities • Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development • Fragmented and Burdensome Data Landscape	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Framework published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, regulated industry, medical researchers, patient organizations, clinical research organizations, privacy lawyers, data/AI companies
15. Clarify Evidentiary Requirements for Utilizing Legacy Registry Data	• The Precedent Paradox • Translation Gap Between Principles and Operational Realities • Unclear Pathways for Disease-Agnostic Endpoints and Measurement Tools Development • Fragmented and Burdensome Data Landscape	**Stakeholder workshop(s)** FDA public meeting with public speakers and public comment period (addressing targeted topics and enabling discussion to yield substantive solutions)	Guidance published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, regulated industry, medical researchers, patient organizations, clinical research organizations, privacy lawyers, data/AI companies

Advancing Shared Understandings of Evidentiary Expectations and Regulatory Requirements

Recommendations	Challenges	Next Steps*	Product	Stakeholders
16. Promote Shared Understandings of Scientific Principles Supporting Flexible Evidentiary Strategies	• Lack of Clarity on Scientific Principles Driving Different Evidentiary Expectations and Regulatory Requirements	**Stakeholder workshop(s)** FDA public meeting with public speakers and public comment period (addressing targeted topics and enabling discussion to yield substantive solutions)	Frameworks updated and/or published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, ICH, regulated industry, patient organizations, medical researchers
17. Enable Early Identification and Resolution of Issues for Novel Endpoints and Trial Designs	• Lack of Clarity on Scientific Principles Driving Different Evidentiary Expectations and Regulatory Requirements	**Stakeholder workshop(s)** FDA public meeting with public speakers and public comment period (addressing targeted topics and enabling discussion to yield substantive solutions)	Rare disease meeting best practices or guidance published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, regulated industry, medical researchers (including statisticians), patient organizations

18. Enable Rare Disease Clinical Trials to Learn and Adapt More Effectively	• Successfully Incorporating Learnings Generated During a Clinical Trial	**Stakeholder workshop(s)** FDA public meeting with public speakers and public comment period (addressing targeted topics and enabling discussion to yield substantive solutions)	Best practices and/or framework published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, ICH, regulated industry, patient organizations, medical researchers (including statisticians)
19. Define Evidentiary Thresholds for Rare Disease Second- and Third-Line 3rd Line Treatments	• Successfully Incorporating Learnings Generated During a Clinical Trial	**Stakeholder workshop(s)** (addressing targeted topics and enabling discussion to yield substantive solutions)	Framework published by FDA, case studies, peer-reviewed publications (illustrating reasons for success and failures)	FDA, ICH, regulated industry, patient organizations, medical researchers

Improving Cross-Stakeholder Knowledge Management

Recommendations	Challenges	Next Steps*	Product	Stakeholders
20. Build a Cross-Stakeholder, AI-Enabled, Rare Disease Knowledge Management System	• Difficulty Translating Siloed Knowledge Management Improvements into Broader Public Benefit	**Stakeholder workshop(s)** FDA public meeting with public speakers and public comment period (addressing targeted topics and enabling discussion to yield substantive solutions)	A publicly available, easily searchable, government housed (or government-adjacent), AI-enabled rare disease knowledge management system	FDA, regulated industry, medical researchers, patient organizations, clinical research organizations, privacy lawyers, data/AI companies

*** Bold and Purple Text = Potential Reagan-Udall Foundation for the FDA Led Activity**

APPENDIX B
Glossary

6MWT	Six-Minute Walk Test
AI	Artificial Intelligence
ALS	Amyotrophic Lateral Sclerosis
ARC	Accelerating Rare Disease Cures
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CHOP	Children's Hospital of Philadelphia
COA	Clinical Outcome Assessment
COU	Context of Use
CRL	Complete Response Letters
CT	Computed Tomography
DDT	Drug Development Tool
DMD	Duchenne Muscular Dystrophy
EMA	European Medicines Agency
FAIR	Findable, Accessible, Interoperable, and Reusable
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GA4GH	Global Alliance for Genomics and Health
GAS	Goal Attainment Scaling
HINE	Hammersmith Infant Neurological Examination
ICH	International Council of Harmonisation
INTEND	Infant Test of Neuromuscular Disorders
IRT	Item Response Theory
LEADER	Learning and Education to Advance and Empower Rare Disease Drug Developers
MCID	Minimally Clinically Important Difference
MRI	Magnetic Resonance Images
NFL	Neurofilament Light Chain
ObsRO	Observer-Reported Outcome
OOPD	Office of Orphan Products Development
ORCA	Observer-Reported Communication Ability
PDS	Project Data Sphere
PED	Patient Experience Data
PFDD	Patient-Focused Drug Development
PRO	Patient-Reported Outcome
RAR	Response-Adaptive Randomization
RDCA-DAP	Rare Disease Cures Accelerator Data and Analytics Platform
RDEP	Rare Disease Evidence Principles
RDPPC	Rare Disease Policy and Portfolio Council
RISE	Rare Disease Innovation, Science and Exploration
RWE	Real-World Evidence
SMA	Spinal Muscular Atrophy
SOD1	Superoxide Dismutase 1 Gene
SVR	Spleen Volume Reduction
TFT	Timed Motor Function Test

APPENDIX C
FDA Regulatory Pathways Supporting Rare Disease Drug Development

This appendix summarizes key FDA regulatory pathways relevant to rare disease drug development and describes how these programs interact with clinical trial design, endpoint selection, and evidence generation. It also identifies areas where additional FDA guidance or flexibility could further facilitate efficient, patient-focused development while maintaining regulatory rigor.

1. Accelerated Approval (AA)

Program Description: Accelerated Approval allows FDA to approve drugs for serious or life-threatening diseases based on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict clinical benefit. Approval is contingent upon postmarketing confirmatory studies to verify and describe the anticipated clinical benefit.

Where to find on the FDA website:

- Accelerated Approval Program (Drugs): https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program
- Accelerated Approval overview (Patients): fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/accelerated-approval
- Table of Surrogate Endpoints Used for Approval or Licensure: fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure
- Expedited Programs for Serious Conditions—Drugs and Biologics (Guidance): fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

Interaction with Trial Design and Evidence Generation: Interaction with trial design, endpoint selection, and evidence generation

AA can enable smaller or shorter trials in rare diseases where traditional clinical outcomes are impractical due to long disease courses or limited populations. This pathway places substantial emphasis on endpoint selection, as the surrogate or intermediate endpoint serves as the primary basis for approval and must be supported by biological plausibility and adequate measurement properties. Evidence generation is explicitly lifecycle-based, requiring sponsors to plan for confirmatory studies at the time of approval.

Gaps and Opportunities: In rare diseases lacking validated biomarkers, sponsors face uncertainty regarding evidentiary thresholds for surrogate endpoints. Additional FDA guidance on acceptable surrogate development strategies and feasible confirmatory study designs particularly when randomized trials are not possible could further facilitate rare disease development.

2. Breakthrough Therapy Designation (BTD)

Program Description: BTD is intended to expedite the development and review of drugs for serious conditions when preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on one or more clinically significant endpoints.

Where to find on the FDA website:

- Breakthrough Therapy Designation overview: fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy
- Expedited Programs for Serious Conditions—Drugs and Biologics (Guidance): fda.gov/regulatory-information/search-fda-guidance-documents/expedited-programs-serious-conditions-drugs-and-biologics

Interaction with trial design, endpoint selection, and evidence generation
BTD facilitates early and frequent FDA interaction, which can be particularly impactful in rare diseases by enabling earlier alignment on trial design, endpoint strategy, and evidentiary expectations. The designation places emphasis on endpoints that are both clinically meaningful and interpretable, even when evidence is preliminary. Early engagement under BTD can reduce downstream development risk by clarifying what constitutes substantial improvement in the context of limited data.

Gaps and opportunities
In rare diseases with heterogeneous clinical trajectories, additional FDA examples illustrating how substantial improvement is assessed across small and variable populations would improve predictability. Greater transparency around acceptable tradeoffs between effect size, uncertainty, and durability of response could further enhance the utility of BTD.

3. Orphan Drug Designation (ODD)

Program Description: ODD applies to drugs and biologics intended to treat, diagnose, or prevent rare diseases or conditions affecting fewer than 200,000 persons in the United States. The program provides incentives to encourage development, including tax credits for clinical testing, user fee waivers, and seven years of market exclusivity upon approval.

Interaction with Trial Design and Evidence Generation: Although ODD does not modify the statutory standard for approval, it supports development feasibility in rare diseases and often enables early investment in natural history studies, patient registries, and patient experience data. These data sources are frequently critical for informing endpoint selection and contextualizing treatment effects when conventional endpoints are not feasible.

Gaps and Opportunities: While ODD incentivizes development, sponsors continue to face uncertainty around endpoint acceptability. Additional FDA guidance linking patient relevance, endpoint selection, and evidentiary expectations—particularly for functional and patient-reported outcomes—could further enhance the impact of ODD in rare disease development.

4. Plausible Mechanism Framework

The FDA published guidance, Considerations for the Use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause, in February 2026. The guidance states, "The plausible mechanism framework outlines a set of recommendations to help developers of individualized therapies generate sufficient clinical safety and efficacy data to demonstrate that a drug or biological product is safe and effective for the intended use, and that the product can be manufactured to regulatory quality standards. These data are used to support approval or licensure of an individualized therapy for a specific indication. This includes a careful evaluation of the results of nonclinical and clinical data and chemistry, manufacturing, and controls (CMC) data necessary to support product quality."

The guidance further stated that the application of the plausible mechanism framework involves the following:

- Identifying a specific genetic, cellular, or molecular abnormality with a clear connection between specific alteration and disease indication
- Developing a therapy that targets the underlying or proximate pathogenic biological alterations
- Relying on a well-characterized natural history of the disease in an untreated population
- Confirming that the target was successfully drugged, edited, or both
- Demonstrating improvement in clinical outcomes or course

Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause

In addition to the 2026 guidance, FDA Commissioner Makary and CBER Director Vinay Prasad published a paper in the New England Journal of Medicine in 2025 describing the plausible mechanism framework.

Vinay Prasad, M.D., M.P.H., and Martin A. Makary, M.D., M.P.H. (2025) New England Journal of Medicine; 393:2365-2367. DOI: 10.1056/NEJMsb2512695

An Example of Patient-Relevant Endpoints and Rare Disease Regulatory Pathways

Luxturna as an Example of Patient-Relevant Endpoints and Rare Disease Regulatory Pathways

Luxturna (voretigene neparvovec) provides an example of how patient-relevant concepts can be operationalized into regulatory-grade endpoints while leveraging established rare-disease regulatory pathways. Developed for individuals with inherited retinal dystrophy caused by biallelic RPE65 mutations, Luxturna's clinical program addressed the limitations of traditional ophthalmic endpoints by introducing the Multi-Luminance Mobility Test (MLMT) which is a functional endpoint designed to assess real-world visual performance under varying lighting conditions.

Luxturna's endpoint strategy originated within an academic research environment.

Investigators at Children's Hospital of Philadelphia (CHOP) and the University of Pennsylvania led the development, validation, and regulatory justification of the MLMT prior to commercial sponsorship. Academic teams generated peer-reviewed evidence demonstrating the MLMT's reliability, sensitivity to change, and clinical interpretability, directly linking performance on the test to patient-identified functional outcomes such as independent navigation and vision in low-light settings. This work was supported by natural history data and iterative methodological refinement, enabling FDA acceptance of the MLMT as the primary endpoint supporting approval.

Luxturna's development pathway also reflects objectives now formalized through initiatives, such as the Rare Disease Endpoint Advancement (RDEA) Pilot Program, including early and transparent engagement with regulators, clear articulation of endpoint context of use, and incremental evidence generation to reduce regulatory uncertainty. Prior to initiation of pivotal trials, the program benefited from multiple FDA interactions, including advisory committee discussions, reinforcing alignment on evidentiary expectations while the sponsor remained academic.

In parallel, the program leveraged several FDA rare-disease regulatory pathways, including Orphan Drug Designation, Breakthrough Therapy Designation, and eligibility for the Rare Pediatric Disease Priority Review Voucher, recognizing the seriousness of the condition and the unmet medical need while maintaining appropriate evidentiary standards for approval. Spark Therapeutics spun out of CHOP in 2013 and assumed sponsorship after foundational endpoint and clinical strategy decisions were already established, highlighting how academic–regulatory collaboration can de-risk development prior to commercialization.

While Luxturna's development involved substantial scientific and regulatory complexity, it may be considered a proof of concept that endpoint-focused, patient-centered approaches may be feasible for drug development programs across other rare diseases.

APPENDIX D

Recent Rare Disease Meetings (2024–2025)

This appendix summarizes recent discussions across FDA, National Institutes of Health, and policy organizations in 2024–2025, which continue to highlight challenges related to endpoint development, trial design, use of real-world data, and global regulatory alignment.

Meeting / Event	Organizer(s)	Year	Purpose / Key Themes
Rare Disease Innovation, Science, and Exploration (RISE) Workshop Series	FDA Rare Disease Innovation Hub + Duke-Margolis Institute for Health Policy	2025	Multisession workshop examined key challenges in conducting clinical trials in rare diseases, particularly in small and diminishing patient populations.
RARE Drug Development Symposium	Global Genes + Boston Children's Hospital	2025	Aimed to equip rare disease patient advocates with the knowledge, skills, and connections needed to confidently initiate and advance early-stage research through practical sessions designed to strengthen research strategies and accelerate progress toward new treatments.
Primary Mitochondrial Diseases Virtual Public Workshop	FDA + Reagan-Udall Foundation	2025	Focused on opportunities to optimize therapeutic development for primary mitochondrial diseases and best practices in designing and interpreting clinical studies that generate meaningful data to accelerate drug development.
Assessing Novel Efficacy Endpoints in Ophthalmic Rare Disease Illness	FDA + Duke-Margolis Institute for Health Policy	2025	Focused on novel efficacy endpoints for drugs/biologics in severe vision loss rare diseases to support regulatory evaluation and decision-making.
FDA Rare Disease Day Public Meeting	FDA + NIH	2024	Annual convening highlighting scientific, clinical, and regulatory issues across rare diseases with a focus on patient experience and development challenges.
Natural History Studies and Registries in the Development of Rare Disease Treatments Hybrid Public Workshop	FDA + Reagan-Udall Foundation	2024	Examined how registries and natural history studies can support rare disease drug development and clinical trial design, with a focus on generating data that are fit for regulatory use and inform regulatory decision-making.
The EveryLife Foundation Scientific Workshop	EveryLife Foundation	2024	Convened stakeholders across the rare disease ecosystem to examine case studies, identify evidence and policy gaps, and develop practical recommendations to advance rare disease therapy development and regulatory decision-making.
Advancing Rare Disease Therapies Through an FDA Rare Disease Innovation Hub	FDA + Reagan-Udall Foundation	2024	Convened rare disease advocacy groups, academia, industry, and other stakeholders to discuss how the newly announced Hub should engage the rare disease community and prioritize its work.

APPENDIX E
Roundtable Contributors

We appreciate the contributions of the following individuals to the Roundtable. While all had the opportunity to review the draft report, their inclusion does not represent their endorsement of or agreement with the content of this report, either individually or on behalf of their organization. The Reagan-Udall Foundation for the FDA retains sole responsibility for this report.

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