

Individualized Therapies on the RISE

November 20, 2025, 9:00 am – 5:00 pm ET

Hybrid Public Meeting | National Press Club

Workshop Summary

Executive Summary

The current drug development paradigm and associated regulations were designed to test single medicines that treat numerous patients, long before the concept of precision medicine became a reality in the form of individualized therapies (e.g., genome editing products and antisense oligonucleotides [ASOs]). Individualized therapies, for this meeting, are defined as therapies tailored to the unique genetic variants of one or a very small number of individuals. While ASOs are not a new technology, their application as individualized therapy is a more recent development. The first individualized ASO treatment was administered in 2018 to treat a form of Batten disease, and more patients with various conditions have received such treatments since that time. Individualized gene editing therapies represent potential medical breakthroughs, including the one used to treat an infant with CPS1 deficiency. The U.S. Food and Drug Administration (FDA) has developed numerous guidance documents for gene therapies and ASOs, including for individualized ASOs. As individualized ASOs and gene editing products are entering the clinic, it is timely to evaluate whether current regulatory practices are optimal to support the development and commercialization of individualized therapies.

This public workshop, co-convened by the Duke-Margolis Institute for Health Policy and the FDA Rare Disease Innovation Hub (RDIH), examined the emerging science and regulatory environment for these individualized medicine programs, including nonclinical data recommendations, clinical data recommendations, regulatory submission structure, and additional information necessary to support the development, evaluation, and potential commercialization of these treatments.

From the day's presentations and panel discussions, the following themes emerged:

- Generating and sharing high-quality data to establish efficacy and safety is critical to support the continued availability of individualized therapies for future patients and potential commercialization.
- Patient/caregiver perspective is essential for defining benefit and understanding tolerance for risk.
- N-of-few clinical trials will require flexibility in trial designs.

- Data sharing and, when appropriate, integrating data from similar patients' treatments can catalyze continuous learning and support commercial viability.
- Bridging a path to commercialization and reimbursement is an important next step.

Participants raised several recommendations, including the need to improve access to individualized therapies through payment and reimbursement mechanisms; clarifying where a full process validation versus a risk-based approach is necessary for platform components in used manufacturing, while distinguishing requirements between ASOs and CRISPR technologies; and the creation of a formal regulatory guidance on the steps to approval of a marketing application, taking into consideration potential opportunities to incorporate innovative trial designs.

Background

The FDA's statutory mandates are to ensure therapies are safe and effective for their intended use. The small and heterogeneous nature of rare disease populations poses challenges in applying the agency's usual approaches for the assessment of safety and efficacy. The agency's experience with evaluating individualized therapies began with ASOs developed for a patient named Mila, who had a form of Batten's disease, and has expanded to other rare diseases. Since then, gene editing therapies have gained traction and shown promise in targeting unique genetic variants. While the Center for Drug Evaluation and Research (CDER) regulates ASOs and the Center for Biologics Evaluation and Research (CBER) regulates gene editing therapies, such as gene editing products, both Centers work collaboratively on their approaches to individualized therapies. However, the unique technological and mechanistic aspects of ASOs and gene editing therapies may have different regulatory considerations for each Center. Most recently, the FDA announced a "Plausible Mechanism Pathway" for the commercialization of individualized therapies, for which implementation plans are in development.

Individualized therapies are often referred to as "n-of-1." However, knowing the exact number of patients who ultimately may be treated with any given individualized therapy is challenging. Therefore, throughout this summary, individualized therapy clinical trials will be referenced as "n-of-few" trials. To ensure a common language across the topic of individualized therapies, additional important terms are defined below:

- **Platform technology:** a well-understood and reproducible technology(ies) applied to the development of a product, or series of related products, that consists of the same or highly similar features across development programs.
- **Platform technology designation:** a designation granted by the FDA to an approved technology to streamline the development and review of new products made with that technology.
- **Platform trial:** a type of perpetual trial with multiple treatments assessed for a disease under a master protocol, not necessarily using a "platform technology."

- **Prior knowledge** (both public and platform) can be leveraged by product development programs to streamline submissions and to expedite product development and review of regulatory submissions, thereby leading to quicker approval of products for patients in need.
- **Master protocols:** a trial that is designed to assess multiple drugs or multiple subpopulations under a single protocol. Types of master protocols include:
 - **Umbrella trial:** to study multiple targeted therapies in the context of a single disease.
 - **Platform trial:** to study multiple targeted therapies in the context of a single disease in a perpetual manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm.
 - **Basket trial:** to study a single targeted therapy in the context of multiple diseases or disease subtypes.

Including the Patient Perspective in Benefit-Risk Assessments is Key

Participants noted the complexity of benefit-risk assessment in cases where individualized therapies might be used to treat extremely rare conditions that are severely debilitating or life-threatening. The distinct nature and the clinical course of a given disease are crucial considerations when thinking about a benefit-risk assessment. A shared sentiment among participants throughout the day was that patients should be the foremost consideration when assessing the benefit-risk of a treatment. Further, incorporating patients' needs and experiences into the benefit-risk assessment also involves input from family and caregiver(s), who are intertwined with the patient's experience and needs. Participants acknowledged that administering an investigational new drug to a patient is a big risk; however, patients emphasized that, in some contexts, those with extremely rare conditions without alternative treatment options may be more willing to take on risks. FDA participants noted that it would be helpful—and welcomed the opportunity—to hear more from patients about the risks they are willing to undertake, particularly when the benefit may be uncertain. Including the patient perspective in interactions with the FDA was a throughline across the event, as tolerance for risk will depend on many factors, including the individual patient and disease severity.

The benefit-risk assessment was also discussed by participants in the context of the clinical setting, focusing on how the patient perspective can be prioritized. Panelists highlighted that improvement and quality of life may look different for each patient. Clinicians play an important role in helping patients assess the benefits and risks of an individualized therapy. One participant emphasized the need for standardized approaches to assessing benefit and risk, and capturing all relevant outcomes.

By including the patient in the benefit-risk discussion, clinical outcomes become central to the conversation. Improvement in a patient's life is an individualized assessment and can

include many considerations, such as the effort it takes to access the treatment, potential adverse reactions, and the impact on their family. Panelists underscored that what matters to the patient should be fundamental in the decision-making process.

Risk Tolerance

Several participants spoke of the assessment of potential risks of a therapy based on data from nonclinical studies. Multiple presenters emphasized that, when assessing risks based on nonclinical data, it is essential to consider both the potential risk of the investigational therapy and the risk of the disease itself, which, if left untreated, could be severely debilitating or deadly. Additionally, multiple speakers suggested that if a risk is known to be related to a specific treatment modality (e.g., gene editing therapies or ASOs) and patients consider this risk to be acceptable given the potential for benefit, regulators could explore reducing redundant nonclinical studies.

N of Few Clinical Trials Will Require Flexibility in Trial Designs

A traditional, randomized controlled trial is often infeasible for very small, heterogeneous, rare genetic disease populations. Participants highlighted that stakeholders have historically tried to fit rare diseases into traditional clinical trial designs developed for more prevalent conditions, rather than designing trials to fit the needs of rare disease patients. Additional challenges that rare disease clinical trials face are sparse natural history and outcome data, challenges in diagnosing and identifying patients eligible for clinical trials, retaining patients in studies, and uncertainty around treatment effects given underpowered studies. These obstacles are heightened for individualized therapies or trials with especially small patient sample sizes. One participant shared the perspective that it's a false dichotomy to consider n-of-1 diseases as distinct from n-of-few diseases. Understanding related diseases and designing flexible trials (e.g., master protocols, umbrella trials), particularly in the individualized therapy space, can help expand measures and potentially support future therapy development.

Recruitment and retention are common reasons for rare disease trial failure, which can be directly linked to trial design. The design of clinical trials in rare diseases should take into consideration the unique challenges of conducting studies in heterogeneous diseases with only a few patients. Participants voiced that new approaches to clinical trial design could improve the patient experience and reduce the burden of participation by leveraging existing data, minimizing the use of placebos, and measuring concepts that are meaningful to patients. In particular, there is a need to identify potential clinical outcome assessments early and develop baseline data before initiation of a therapy so that patients can move into a clinical trial with established data on the course of their disease.

Trial designs that could better fit the needs of rare disease populations include baseline-controlled studies to measure pre- and post-intervention changes and the use of master protocols to reduce the use of placebos. Participants described Bayesian statistical methods and using natural history data to supplement the placebo group so that more

participants in the clinical trial can be randomized to the active treatment. Regulators highlighted that the inclusion of natural history data as part of a control group requires forethought and pre-planning for the data to be robust enough for inclusion. Audience engagement highlighted the potential of serial, baseline-controlled studies to measure pre- and post-intervention changes. Such an approach would require pre-specifying which outcomes should be measured based on discussions with the patient, their family, and their care team about what would be a meaningful change. This has the potential to demonstrate quantitative benefit in a way that may also be informative for payors, who will be important stakeholders for commercialization and expanding individualized therapies to broader populations.

Data Sharing and Integration Can Catalyze Continuous Learning and Support Commercial Viability

Discussion throughout the day highlighted the need for increased data sharing and integration to support innovation, and highlighted data generation, sharing, and iterative learning as core to responsible innovation. Stakeholders have historically approached n-of-few therapies as treating individuals rather than contributing to a larger evidence base, but there may be commonalities across development programs that can generate transferable knowledge to other patients. The utility of data sharing and integration is dependent on the generation of high-quality data based on rigorous, systematic data collection and the creation of data storage and sharing systems. Panelists discussed that there is not currently a system or resource for transferring knowledge among different stakeholders in the individualized therapy space, with some advocating for data sharing to support continuous learning and commercial viability.

Discussion focused on how collating data on like-diseases can advance trial design and endpoint innovation, while optimizing treatment effects and scaling solutions beyond individual use cases. Participants called out urea cycle disorders as a strong example of how similar molecular pathophysiology can inform like-disease research and enable use of master protocols that could increase learnings on biomarkers, safety, efficacy, patient-reported experiences across a variety of similar conditions. Discussion also touched on the use of disease registries to support trials. Prior to development or initiation of treatment with an individualized therapy, a disease registry may serve to identify patients early for future earlier trial enrollment and characterize the course of the disease. Following treatment with an individualized therapy, a disease registry can also be leveraged to collate safety and efficacy data. Panelists also highlighted the role registries play in increasing communication across sponsors and researchers while reducing patient burden due to long-term follow-up.

Speakers emphasized the need for more public sharing of nonclinical and toxicology data. Discussion used adeno-associated virus vectors as an example, highlighting the importance of sharing contextualized fatality rates and other toxicological information with the public.

Sharing toxicology data could help generate community-driven consensus around toxicity. Lastly, panelists discussed the opportunity to utilize ASO data insights to inform academic drug developers, start-ups, and large pharmaceutical manufacturers.

Bridging a Path from Research to Approval and Commercialization

Despite the scientific advances, participants highlighted that there remains a need for a “bridge” to bring more individualized therapies from research to approval and commercialization, which will increase access for the millions of patients who could benefit. The current development approach for individualized therapies was described as inequitable, slow, expensive, and overly dependent on philanthropy and extraordinary personal effort. Discussion touched on how the traditional product development paradigm makes expanding these life-changing therapies to broader populations extraordinarily difficult. Discussion also focused on how expanding from n-of-1 cases to larger clinical trials across patients and disease manifestations will require practical and ethical considerations, as well as payor engagement.

Payor involvement

Discussion highlighted the end goal of commercialization to sustainably support access to individualized therapies for more patients. Panelists emphasized the need for both regulatory approval and reimbursement. A clear regulatory path to marketing authorization was identified as essential for reimbursement. Without regulatory approval and confidence in clinical outcomes, participants explained that payors will lack the necessary scientific and financial information to support reimbursement. Approving products without reimbursement disincentivizes scaling development and slows clinical innovation.

Early engagement with payors on the data needed to support reimbursement is critical. Identifying clinically meaningful patient endpoints for reimbursement was acknowledged as an important step. Participants explained that payors consider carefully how they spend public or employer dollars—especially for very high-cost therapies—so they’ll look for strong guaranteed, measurable outcomes. Master protocols also offer an opportunity for stakeholders to thoughtfully engage with payors to make designing trials that are more informative and cost-effective in the long term.

Discussion also touched on the need to pivot from framing individualized medicines as “research” to presenting them as evolving treatments and technologies that are viable and appropriate options for reimbursement. One panelist suggested that rather than examining each medicine case-by-case, the field should present individualized therapies as advancements in clinical outcomes paid off by prior investments in genomic research, such as the Human Genome Project, to secure major pooled funding and attract matching

private investment for another large-scale, coordinated national program to create a sustainable ecosystem for these therapies.

Pathway to approval

Discussion focused on a potential path to approval based on evidence from trials of an individual patient or few patients meeting a predetermined, measurable outcome. Panelists also suggested a process-based approval path, where a rigorous, validated process for developing safe, high-quality individualized therapies is approved rather than approving each individualized therapy as a standalone product. Furthermore, panelists discussed that if this process was standardized and shown to produce safe, beneficial treatments, it should be commercially approvable and reimbursable. Discussion highlighted that a new, tailored, end-to-end pathway is needed to translate emerging individualized medicine capabilities into real-world patient access, and that no single organization (regulator, industry, clinicians, payors, or patients) can create a new pathway alone. Panelists called for formal guidance outlining a route to approval, stating that current guidances may not address potential for future licensure or approval of individualized therapies.

Manufacturing

Participants explained that n-of-few commercial manufacturing cannot be retrofitted into the large-scale pharma paradigm, and that a new model is needed with a clear line of sight to commercialization. The lack of a clear benefit-risk framework for commercial manufacturing, even though frameworks exist for first-in-human clinical production, was highlighted as the major manufacturing challenge for individualized therapies. Discussion touched on how the current benefit-risk approach for commercial launch requires manufacturers to consider which parts of the product provide enough incentive to complete quality control analyses. Participants also highlighted the recent example of an infant with CPS1 deficiency to show how individualized therapies rely on multi-partner, modular platform technologies, where some components (e.g., LNP, base editor mRNA) could be reused across many patients while others (e.g., the guide RNA) are patient-specific. For commercialization, panelists suggested that regulators need to clarify which platform technology components need full process validation and where a risk-proportionate approach can be applied to avoid unnecessary studies. Discussion also focused on platform technology approaches—sharing elements such as manufacturing steps, vectors, editors, or other chemistry, manufacturing, and control elements—and how this could substantially streamline development across different patients and mutations. Panelists suggested that if the FDA platform designation was not limited to companies that already have an approved commercial product, this would stimulate investment in critical component platform suppliers. Discussion highlighted that most individualized therapy

manufacturing partnerships to date have involved academics, nonprofits, technology providers, and small-scale manufacturers and not large industry; panelists emphasized the importance of keeping nontraditional product sponsors in mind when designing regulatory and reimbursement pathways. Furthermore, participants explained that initial guidance documents were written for academic investigators, focusing on minimal manufacturing and non-clinical requirements, not imagining that there would be commercial potential for individualized ASOs.

Next Steps and Future Work

Recommendations

Panelists and participants made recommendations for future work to improve access to individualized therapies throughout the workshop, with the overarching theme of needing to efficiently approve these therapies. Panelists called for a change in how to view benefit-risk assessments for individualized medicines, suggesting that patients, families, and patient communities should be more involved in these decisions. They also identified the need for pre-defined and standardized efficacy data collection. Discussion highlighted payment recommendations, specifically emphasizing the need to pivot individualized therapies from research to treatment to allow for reimbursement, and calling for a comparable workshop on rare disease therapy reimbursement and payment considerations. Data sharing and integration between like-diseases, especially for toxicity and safety data, was suggested as critical for advancing and expanding the use of individualized therapies. Clarity is needed on where a full process validation versus a risk-based approach is necessary for platform components in manufacturing, along with a new tailored paradigm for manufacturing in this space. Speakers called for more formal regulatory guidance that outlines clear steps to approval and to explore the use of innovative trial designs or process approvals to reduce patient and trialist burdens, share data, and expand access to individualized therapies. Additionally, speakers noted the need for greater clarity in regulatory distinctions between ASOs and CRISPR technologies.

Next steps

This workshop served as the second in a series of Rare Disease Innovation, Science, and Exploration (RISE) Workshops on rare diseases and serves as one mechanism to accomplish the stated goals of the FDA RDIH. The third workshop, scheduled for March 30, 2026, will focus on data sharing across the rare disease ecosystem. We encourage anyone interested in the RDIH and future RISE Workshops to submit comments or ideas to the [FRN](#) to support future work/workshops.

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