Dear Ms. Roth,

On behalf of the more than 25 million Americans living with one of the over 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency’s draft guidance, “Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints for Regulatory Decision-Making.”

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded 40 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing that landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to safe and effective therapies. Supporting patients, drug sponsors, and the FDA in patient-focused drug development (PFDD) activities has been a long-standing priority for NORD in pursuit of our ultimate goal - to improve the lives of individuals and families affected by rare diseases.

NORD commends the Agency for its sustained implementation of the mandates under the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act (FDARA) to promote the patient voice in the therapeutic development process. We were pleased to help craft these legislative and regulatory proposals, and we submit these comments on the fourth of FDA’s series of guidance documents on this issue in the hopes of assisting the Agency in its continuing initiatives.

Strengths and Limitations of the COA-Based Endpoints

The Agency’s guidance on how to construct endpoints that will support inferences about a drug’s effect on patients is useful for sponsors and investigators, including rare disease patients and advocacy groups currently pursuing foundational research, early-stage drug development, and the generation of patient experience data. In addressing the “strengths and limitations” of proposed endpoints, however, the guidance describes how experience with a given endpoint in one trial for one disease may not suffice to support its subsequent use because of the time elapsing between the two trials, as well as the “context of
use” in different diseases.\(^1\) NORD encourages the Agency to balance this assertion by acknowledging that developing and validating a fit-for-purpose Clinical Outcome Assessment (COA) for a rare disease with a small, heterogeneous patient population, with limited available data on natural history and disease progression, or for a new and poorly characterized disease variant or population subgroup, presents unique challenges. For instance, the underlying assumptions of normality in the data analysis are likely to work for common diseases with large sample sizes but are less likely to work for small sample sizes in rare diseases. In addition to the balance of validating fit-for-purpose COAs for rare diseases, more clarity is needed on the data needed to validate the endpoints and when extrapolation of these endpoints is feasible, especially in the cases of rare diseases. Creation or refinement and application of rare disease COAs requires sustained flexibility to avoid the risk of inadvertently signaling unrealistically high regulatory hurdles, which may further deter COA development, particularly for rare diseases.

**Rare Disease Examples of Constructing COA-Based Endpoints**

NORD has emphasized in its previous comments to this series of guidance documents that the rare disease community needs more practical guidance to give appropriate direction for how to create and validate COAs for rare diseases. Providing concrete examples and discussions of fit-for-purpose as well as unacceptable or deficient COAs, either through revision of the guidance or through subsequent implementation activities (see below), would provide the rare disease community with much needed practical guidance and give appropriate direction for how to create rare disease COAs as well as adopt and support evidence generation using accepted or validated COAs.

This is particularly true for the discussion of the construction of COA-based endpoints and of multiple and multiple-component endpoints.\(^2\) Illustrative examples of robust, fit for purpose and validated endpoints would help clarify how to overcome issues endemic to rare disease drug development. For the case of rare diseases, single-arm trials are more likely to be used than common diseases. The intended audiences would be sufficiently informed not to take such examples as exclusive manifestations of the COAs and endpoints that can reflect patient health or demonstrate treatment effects.

In addition, the guidance notes the use of change-from-baseline endpoints, which may not work given lack of natural history/disease progression and heterogeneity in response.\(^3\) In addition to the recommendations from this guidance, the RDEA Pilot Program from FDA aims to support the development of novel endpoints for the development of rare disease drugs. Preliminary learnings and findings, when applicable, from the RDEA Pilot Program should be incorporated in the final guidance to further support more evidence on when to use multi-component and composite endpoints for rare disease drug development. Given the complexity of rare diseases, small patient populations, and lack of natural history studies, more guidance and strategies are needed in using alternative, multiple, co-primary, and singular endpoints.

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\(^2\) Id. Pp 6-13.

\(^3\) Id pp 8.
Patient Experience and Patient-Based Strategies in Mitigating Missing Data

NORD supports FDA’s discussion of the types of missing data that can degrade evidence based on COA-based endpoints. In describing the methods and procedures that investigators and sponsors can use to avoid missing data, NORD believes that additional encouragement is warranted to seek and utilize the practical and methodological experience that patient groups may have in securing timely feedback, encouraging participant compliance, factors underlying drop out, and ways to mitigate challenges and barriers that underlie missing data.

In addition, the guidance should expand the real-world limitations to consider rare diseases, as it is not uncommon for a diagnosis to impact multiple aspects of feeling and functioning. By adding engagement for rare diseases, this can better inform the design of patient-focused trials for more patients, but also improve the collection of data overall. In addition, decentralized and virtual trials need to be researched more in collecting patient data for COAs, especially in the case of rare diseases. Given the smaller populations and unique disease manifestations, allowing participants to participate virtually or closer to home can allow for more data to be used. NORD believes that the addition of specific strategies, procedures, and operational relationships or partnerships with patients and their advocacy groups, that have helped promote the successful use of COA-based endpoints in clinical trials would strengthen the draft guidance.

Reliance on Patient Validation of Measurement of Patient Experience

The draft guidance gives due weight to COAs that “measure a concept of interest that is a directly interpretable reflection of the patients’ health-related experiences.” It is notable that an example provided, “an ordinal” or “PRO measure of current pain intensity”, is used to illustrate laudable measures of “feeling and functioning” that are “well understood” and easy to interpret. In addition, more guidance is needed on how patient experience data relates to COA scores. By providing this transparency to patients, they will be able to understand how their experiences can be turned into data. NORD encourages the Agency to provide additional examples that are disease-specific or disease group-specific, which would assist sponsors and investigators in understanding COAs and endpoints that are viewed as capturing meaningful outcomes for specific conditions or diseases.

The Agency should consider more research into the appropriate use of personalized endpoints for rare disease drug development, as the same diagnosis can manifest uniquely in different individuals. Given the paucity of rare disease-specific patient-centered outcome measures, the selective addition of such examples for rare diseases would assist the audiences in better understanding what is acceptable and desirable from a regulatory standpoint.

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4 Id pp 17.
5 Id pp 19
6 Id pp 9
7 Id pp 33
Implementation and Engagement to Promote Understanding and Use of FDA’s PFDD Guidance Documents

NORD agrees strongly with FDA that sponsors “engage with patients… when designing and implementing studies to evaluate the burden of disease and treatment, and perspectives on treatment benefits and risks.” Close partnership and collaboration between FDA, patient advocacy organizations, and other key stakeholders will be key to ensuring that rare disease patient advocacy groups assume a more active role in developing COAs and that sponsors and investigators develop and adopt such COAs efficiently into drug development programs. To facilitate and ensure consistent implementation of the Agency’s recommendation for rare disease drug development, we urge the Agency to:

- Pursue different avenues to expedite the development, acceptance, and sharing of COAs for rare diseases, through public meetings, public-private partnerships, and pilot grant programs; and
- Support the development of educational materials and related supporting tools specific to the development, statistical issues of COAs, adaptation, validation, and use of fit-for-purpose COAs in rare disease drug development, such as instructional videos, case studies, and discussion guides for asynchronous learning as well as potentially workshops, presentations, and FDA listening sessions for synchronous learning that are fit for a patient advocate audience.

NORD believes strongly that this unique series of guidance documents will not have their full and beneficial effect on drug development for rare diseases unless the Agency follows through with sustained stakeholder discussion and engagement, especially efforts to encourage the sharing of best practices and successful development programs, as well as targeted educational programs for rare disease patients, their providers and advocacy groups, on how to best put the Agency’s guidances into practice.

Conclusion

In conclusion, NORD commends the agency for publishing this draft guidance and the entire series of guidance documents which are essential to accelerating the widespread adoption and use of COAs in drug development programs and regulatory decision-making. However, we urge FDA to periodically update relevant guidance documents on PFDD and COA with significant detail, best practices and lessons learned specifically for rare diseases consistent with the recommendations outlined within this and previous guidance documents to ensure their full benefit to the rare disease community. We would also be delighted to continue the conversation and support the FDA in this important endeavor as possible.

NORD again thanks FDA for the opportunity to provide comments on this important draft guidance, and we look forward to continuing the dialogue around PFDDs, as well as other strategies to bring safe and effective rare disease drugs quickly and effectively to market. For questions regarding NORD or the above comments, please contact Hayley Mason, Policy Analyst, at hmason@rarediseases.org

Sincerely,

Hayley Mason, MPA
Policy Analyst
National Organization for Rare Disorders

8 Id pp 2