September 27, 2022

Lauren K. Roth
Associate Commissioner for Policy
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

RE: FDA's Draft Guidance 'Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders,' Docket No. FDA-2022-D-1385

Dear Ms. Roth,

The National Organization for Rare Disorders (NORD) appreciates this opportunity to comment on the U.S. Food and Drug Administration's (FDA) draft guidance **'Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders.'**

For nearly 40 years, NORD has been dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 325 patient organization members, is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services. 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 applauds FDA's efforts to clarify agency expectations and foster an abundance of clinical outcome assessments (COAs) that are fit for their intended regulatory purpose and adequately capture the patient voice. We appreciate the draft guidance as an important mechanism to improve the quality, availability, and use of clinical outcome assessments as an integral part of rare diseases drug development programs. We offer comments below to assist FDA in ensuring that the guidance is sufficiently instructive and understandable by all its intended audiences, cognizant of data limitations and feasibility constraints for rare diseases and aligned with the right incentives to promote widespread adoption in rare disease drug development.

Rare disease patients and other key stakeholders need additional guidance, education, and support to be effective partners in the development and use of COAs

NORD appreciates the breadth of disease areas and the diverse group of stakeholders,[1] including patients, caregivers, researchers, medical product developers, and others, that FDA seeks to address with this guidance. In the rare disease space, these are the stakeholders NORD works with daily, from our patient assistance programs to our Rare Diseases Centers of Excellence. Each of these stakeholder groups has distinct, heterogeneous educational needs that are difficult to meet through one guidance series.

[1] Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders developers, and others' – Section I.A.

Rare disease patients, caregivers, and their advocacy groups have a critical role in the development and use of COAs. Already rare disease patients, caregivers, and their advocacy groups take on a disproportionate role in furthering foundational research, early-stage drug development, and the generation of patient experience data. Patients devote their scarce time and resources to participate in the clinical trials; their health and quality of life are what is measured in the COAs, and they are the experts on what it means to live with their disease every day. According to a recent NORD survey of 137 rare disease patient advocacy organizations, 75% of organizations currently conduct or are in the process of developing natural history studies, and most of the queried patient advocacy groups are working with relevant industry researchers investigating their disease. That same survey found, 1 in 4 rare disease patient advocacy groups are interested in the development of COAs, but do not know where to begin. Unfortunately, this COA draft guidance provides these highly motivated groups with little concrete advice on how to get started.

Patients and caregivers must be informed partners in the rare disease drug development process and empowered to embrace their unique roles in supporting the collection and submission of meaningful patient experience data. To do so, rare disease patients need to understand the fundamentals of what makes a COA fit for its intended regulatory purpose. Even more important, rare disease patients and caregivers must have realistic and concrete expectations about if, when, and how COAs are adequate to capture the outcomes that matter most to them – and why, in some cases, a COA may not be the best choice. Existing educational materials such as the National Health Council's COA webinar series[2] and FDA's public PFDD webinar on selecting, developing, or modifying fit-for-purpose clinical outcomes assessments[3] are highly valuable and start to lay the important educational foundation that our rare disease community needs, but still leave important knowledge gaps unfilled. Similarly, NORD is already working with FDA and other key partners in the rare disease space to create educational materials that begin to close patients' educational needs around drug development including COAs, but again, important knowledge gaps remain.

NORD is deeply concerned that this very technical and quite abstract guidance document will be too difficult to understand and implement for most rare disease patient and caregiver groups. Based on NORD's long-standing experience supporting rare disease patients, caregivers, and their advocacy organizations with education, research, data collection, and the organization of PFDD meetings and listening sessions, we urge FDA to adopt a multi-pronged strategy rooted in clear communication, implementation support, and educational best practices. We would like to offer the following recommendations to support rare disease patients' educational needs related to COAs.

- In the near term, we recommend FDA consider incorporating a plain language summary in all guidance documents with rare disease patients, caregivers, and patient advocacy groups as one of the key audiences. This would ensure this audience understands which guidance documents are relevant to their issues and where to start looking for further support and instruction.
- In the medium term, incorporating concrete examples and discussions of fit-for-purpose COAs – as well as possibly COAs that are deficient in specific ways - would empower the rare disease community to recognize and advocate for well-done COAs. This could include implementation

[2] https://nationalhealthcouncil.org/additional-resources/clinical-outcome-assessment-coa-webinar-series/
[3] https://www.fda.gov/drugs/news-events-human-drugs/public-webinar-patient-focused-drug-development-selecting-developing-or-modifying-fit-purpose

guides, checklists, and best practices, and could be incorporated in the guidance or presented as stand-alone resources.

- In the longer term, NORD recommends developing educational materials and related supporting tools specific to the development, adaptation, validation, and use of fit-for-purpose COAs in rare disease drug development. To address the unique needs of rare disease patients, caregivers, and patient advocacy organizations hoping to further the development of COAs for their disease area, we recommend FDA considers a variety of potential formats including instructional videos, case studies, and discussion guides for asynchronous learning as well as potentially workshops, presentations, and FDA listening sessions for synchronous learning. This would provide crucial support for the substantial number of rare disease patient advocacy groups that want to assume a more active role in developing COAs, but currently simply do not know where to begin.

Close partnership and collaboration between FDA, patient advocacy organizations, and other key stakeholders will be key to the success of this educational strategy.

Rare disease patients and other key stakeholders need additional guidance on how to address the unique challenges in developing COAs for the small, often heterogeneous populations impacted by rare diseases

COAs must be robust, fit for their intended purpose, and rigorously validated to be meaningful and of value for patient communities and the broad range of stakeholders involved in drug development. However, for rare diseases, what robust COA validation looks like can be highly context specific. Developing and validating a fit-for-purpose 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. In its current form, the draft guidance provides limited discussions on how to overcome the issue associated with small populations and rare diseases. For instance, with rare diseases, COA development, adaptation, and validation may have to occur later in the drug development program than desirable or typical in other disease areas and may be a more iterative process than presented in FDA's guidance. Without clear guidance, regulatory uncertainty remains as to what types of strategies and approaches may be acceptable in developing, adapting, and validating COAs in the rare disease context. Moreover, the new guidance carries the risk of inadvertently signaling unrealistically high regulatory hurdles to creating COAs in such situations, which may further deter COA development, particularly for rare diseases. The rare disease community needs more practical guidance to give appropriate direction for how to create fit-for-purpose COAs for rare diseases – and for when a COA may be unattainable or simply not the best solution.

Based on NORD's long-standing experience supporting research on rare diseases and working with patient organizations on their research readiness, NORD recommends the FDA describe and mature additional and alternative COA tools and approaches, including guidance for their adequate use.

- In the near term, we recommend FDA expands its guidance to include a more detailed and nuanced discussion of how to address and potentially overcome various challenges in COA development, with a particular focus on COAs for rare diseases. For each step in the COA development process, it would be helpful to outline common development challenges, potential alternative approaches for small populations and rare diseases (if any), circumstances under which such alternative approaches may be acceptable, and a discussion of the strengths and weaknesses of each alternative approach. A tiered system, akin to weight-of-evidence

frameworks like GRADE[4] (Grading of Recommendations Assessment, Development and Evaluation), could be developed to try and integrate evidence of varying formats and levels of persuasiveness in a systematic, reproducible, and rigorous way for decision-making.

- In the medium term, as part of the educational materials and implementation guides discussed above, we recommend FDA provides training, best practices, and lessons learned for fit-for-purpose COA development in rare diseases.
- In the longer term, we recommend FDA help further develop regulatory tools, approaches, and best practices specific to COAs in rare diseases. Initiatives such as public workshops, external trainings, and challenge grants can foster progress in regulatory science, as can pilot programs such as the Rare Disease Endpoint Advancement (RDEA) Pilot program outlined in the Prescription Drug User Fee Program (PDUFA) VII commitment letter. Some of these strategies and approaches have been very successful in developing regulatory science in other areas of rare disease drug development and could be applied to rare disease COAs.

In the rare disease ecosystem, the right incentives are key to drive widespread and cross-disease COA development, including the sharing of COAs across academic researchers, drug sponsors, and rare disease communities

Many of the COAs important to rare disease communities are complex and difficult to develop, and limited regulatory precedent exists. For individual rare diseases with particularly small populations, developing and validating robust and fit-for-purpose COAs can be exceedingly time and resource intensive and prohibitively expensive. Moreover, many rare diseases affect multiple organ systems that often require the development of more than one separate COA. NORD therefore strongly supports FDA's efforts to catalogue and share existing COAs, to support the development of multi-disease COAs, and to fund efforts to develop additional COAs. Yet, although these initiatives are important steps in the right direction, additional incentives will be needed to further strengthen the development and use of COAs in rare diseases including the development of COAs for complex 'concepts of interest' such as 'social functioning' or 'quality of life' that are important to many of our rare disease patient communities.

Based on NORD's almost 40 years of experience in advocating for incentives to develop new treatments for rare diseases, we would like to offer the following recommendations.

- In the near term, we urge FDA to further increase funding for COA development, particularly COAs for rare diseases and complex 'concepts of interest.' This funding could be provided through several mechanisms; for instance, as part of the pilot grant program for standard COAs and their related endpoints, or through a public-private partnership focused on COA development for rare diseases and 'complex concepts of interest.'
- In the medium term, we hope FDA, in close partnership with all affected stakeholders, will consider innovative approaches to incentivize the sharing and use of COAs, including the underlying data needed for COA adaptation and validation. A variety of out-of-the-box approaches may prove useful; for instance, sharing COAs (and their underlying data) could become a condition of funding, publication, technical assistance, or patient participation; investigators who voluntarily share their COAs and underlying data could receive public recognition and support; and incentives such as those outlined in the Advancing Real-World

[4] https://www.gradeworkinggroup.org/

Evidence for Use in Regulatory Decision-Making program described in the PDUFA VII commitment letters could be created. In fact, a menu of incentives may prove useful in ensuring the broad sharing of COAs across drug development programs.

In conclusion, NORD commends the agency for publishing this draft guidance on developing fit-for-purpose COAs. Concise, detailed, and specific guidance that clarifies expectations and creates incentives for COA development is paramount to the widespread adoption and use of COAs in drug development programs and regulatory decision-making for rare diseases. We encourage the FDA to finalize the proposed guidance swiftly and to update relevant guidance documents on PFDD and COA periodically with significant detail, best practices and lessons learned. We would also be delighted to continue the conversation and support the FDA in this important endeavor as possible. Please do not hesitate to reach out to Karin Hoelzer, Director of Policy and Regulatory Affairs by email at khoelzer@rarediseases.org or by phone at 202-588-5700 with any questions or requests for further information and clarification.

Sincerely,

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