



August 6, 2019

Division of Dockets Management (HFA-305)  
U.S. Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Docket No. FDA-2019-D-1264 for “Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs.”**

Dear Sir or Madam:

On behalf of the 25 to 30 million Americans 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(NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency’s draft guidance for industry titled “Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs.”

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

The Agency's commitment to meaningful and substantial collaboration with the rare disease community has been unwavering since the enactment of the Orphan Drug Act. It is estimated that there are over 7,000 rare diseases, which are defined in the United States as diseases affecting 200,000 or fewer people. Today, over 90 percent of rare diseases still do not have an FDA-approved treatment indicated to treat the disease. The barriers and significant obstacles that hinder the pursuit of rare disease therapies to meet the substantial unmet medical needs of patients with rare disorders requires the continued partnership of FDA, patients, investigators, and sponsors.

Greater patient involvement in the drug development process is one of NORD’s main priorities. We remain supportive of FDA’s efforts to incorporate the patient perspective in the development of medical products and regulatory product review. Toward that end, we appreciate that the emphasis of this draft guidance is to encourage sponsors to recruit clinical trial participants that will better reflect the population most likely to use the drug. In the rare disease community, targeting patients that will most likely use, and hopefully benefit from, the drug is important.

In this draft guidance, FDA recommends sponsors broaden their eligibility criteria to “maximize the generalizability of trial results and to better understand the therapy’s benefit-risk profile across the patient population.” We appreciate the recommendation to include participants across the full spectrum of disease severity. NORD has previously encouraged FDA and sponsors to

consider broad inclusion criteria and to target all rare disease patient populations that could benefit from a therapy. Moreover, NORD has been supportive of efforts to encourage sponsors to consider individuals with severe or advanced disease, rather than automatically disqualifying them as has happened many times in the past. We are pleased to see these broad inclusion criteria reflected in this draft guidance.

NORD is supportive of FDA's recommendations that sponsors consider a pediatric development program early and also include children and adolescents in confirmatory clinical trials involving adults when appropriate. Many rare diseases begin in childhood, so the benefits of having appropriate treatments available to children cannot be overstated.

In this draft guidance, FDA discusses additional challenges for sponsors to consider when enrolling participants in clinical trials, including frequency of visits to specific sites and burdensome financial costs. We appreciate that FDA explicitly states in the draft guidance that "FDA does not consider reimbursement for reasonable travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence." For many rare disease patients, these logistical and financial hurdles are very real and are a disincentive to clinical trial participation. It is important for sponsors and patients to understand that this type of reimbursement is permissible and will help to encourage clinical trial participation.

Although many factors that impact standard clinical trials also impact rare disease specific clinical trials, rare diseases present some additional unique challenges. NORD is pleased that FDA recognizes this and discusses some of these unique challenges in section IV of the draft guidance. In section IV, FDA suggests that special efforts may be necessary to enroll and retain participants with rare diseases and recommends three specific efforts to sponsors: 1) engagement early in the drug development process with patient advocate groups for input on trial design and participants; 2) consideration of re-enrolling participants from early-phase trials into later-phase trials, if appropriate and being careful of selection bias; and 3) making available an open-label extension study after early phase studies.

Patient perspectives on everything from clinical trial design and endpoint selection to dosing schedules and clinical trial locations can be critical to ensuring that tomorrow's therapies are patient-friendly and patient-focused. Therapies that are developed and reviewed in consultation with patients are much more likely to reflect the needs and desires of the patient population and are more likely to offer greater benefits with fewer risks. Only patients who live with the disease and their caregivers can offer these uniquely important perspectives, and their input should be acquired at the outset. Thus, NORD applauds FDA for recommending that sponsors engage early in the drug development process with patient groups.

Many rare diseases affect small populations, sometimes only a few hundred people. Overcoming unique challenges of testing therapies in small patient populations requires flexibility. This flexibility is critical in both the design and the analysis of clinical trial results. We are pleased that FDA recommends in this draft guidance that sponsors consider re-enrolling participants from early-phase trials into later-phase trials, if appropriate and being careful of selection bias.

We believe that permitting re-enrollment of participants will be helpful to ensuring clinical trials in rare disease populations can continue into the next phase.

Finally, we are particularly supportive of FDA's stated flexibility with various clinical trial structures. By doing so, FDA appropriately offers various alternatives for sponsors to consider. In addition to FDA's recommendation that sponsors consider making available open-label extension studies after early phase studies, NORD encourages FDA to also consider flexibility for single-arm trials that use historical controls based on natural history data. FDA has indicated flexibility for single-arm trials previously.

We thank the Agency again for the opportunity to comment and look forward to working with FDA to ensure rare disease patients and patient advocacy organizations are able to fully participate within this important effort. For questions regarding NORD or the above comments, please contact me at [rsher@rarediseases.org](mailto:rsher@rarediseases.org) or 202-545-3970.

Sincerely,

A handwritten signature in black ink that reads "Rachel Sher". The signature is written in a cursive, flowing style.

Rachel Sher  
Vice President of Policy and Regulatory Affairs