December 30, 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-4247 for "Patient-Focused Drug Development: Methods To Identify What Is Important to Patients."

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(NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance for industry, FDA staff, and other stakeholders titled "Patient-Focused Drug Development: Methods To Identify What Is Important to Patients" ("Draft Guidance").

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.

NORD supports 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 Toward that end, we appreciate that the emphasis of this Draft Guidance is on identifying what matters most to patients in terms of the burden of their disease and treatments. This Draft Guidance suggests ways to engage with patients early in the drug development process. The importance of patient input at the beginning stages of research and development cannot be overstated. To improve upon this Draft Guidance, NORD offers the following general and specific suggestions for FDA's consideration.

The Draft Guidance describes patient focused drug development meetings as one example of facilitated discussions to obtain patient perspectives. In September 2019, NORD held its first externally-led patient-focused drug development meeting on pyruvate kinase deficiency (PKD).

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During this meeting, patients and caregivers described the burdens of living with PKD and some of the challenges with the existing treatments. To engage participants to the fullest extent, NORD utilized a mixed-method approach, incorporating the collection of both qualitative and quantitative data from participants. This approach worked well and elicited in-depth input from patients on the burden of living with their disease and what they would like to see in new treatment developments. Using mixed methods, 100 percent of patients (participating both in-person and online) indicated they have received a blood transfusion, patients and caregivers revealed that many patients, particularly children, suffered from post-traumatic stress disorder (PTSD) due to the trauma of repeated blood transfusions, and many patients ranked reduction in the need for transfusions as one of the most important endpoints when selecting a new treatment for PKD. As evidenced by this meeting, patient-focused drug development meetings have been a critical tool in identifying the burden of disease and existing treatments, and patient preferences for new drug development.

Natural history studies are another valuable mechanism for collecting patient experience data. These studies are designed to be longitudinal and can help to centralize small rare disease populations on a common platform. Additional one-time data collection or studies that have a defined project period can be supported and recruitment for both quantitative and qualitative research can benefit from the framework for a natural history study.

In 2014, NORD launched a patient-driven rare disease natural history study platform called the IAMRARE™ registry program. This innovative system positions NORD in a unique and strategic role to advance the science of rare disease drug development. The platform was designed with extensive input from FDA, the National Institutes of Health (NIH), patient advocacy organizations, and other public health experts. It now hosts over forty rare disease natural history study partnerships, twenty of which were developed in part due to a cooperative agreement with FDA (U24 FD005664).

The IAMRARE™ registry program works in collaboration with patient advocacy organizations and industry partners to capture natural history data that accomplishes the following goals: 1) supports drug development by characterizing and fostering increased understanding of the natural progression of rare diseases and the corresponding burden on patients; 2) acts as a resource for patient cohorts for clinical trials; 3) supports pre- and post-market surveillance; and 4) fosters the development of clinical outcome assessments (COAs). When discussing natural history studies, we ask FDA to consider recommendations that support data use, access, and ownership that allows for a variety of stakeholders to benefit from the information. We appreciate that FDA is working to finalize the draft guidance titled “Rare Diseases: Natural History Studies for Drug Development Guidance for Industry.” However, we strongly recommend that in this guidance, FDA elaborate on the benefits of natural history studies to identify what is important to patients.

Patient Listening Sessions, hosted in a collaboration between FDA Patient Affairs Staff and NORD, provide an additional pathway for the FDA to understand what is important to patients and caregivers to support and inform regulatory decision-making, provide foundational information for early stage research and development, and to educate FDA review staff about patient experiences with specific aspects of rare diseases. We recommend that the FDA include

more detail about the benefits of Patient Listening Sessions and a recommendation in this guidance for the use of Patient Listening Sessions as a tool for identifying what is most important to patients early in the research and development process.

With every aspect of drug research and development, early interactions are key. Toward that end, NORD supports FDA's recommendation that stakeholders have early interactions with FDA and the relevant review divisions when collecting patient experience data. Yet, more specific guidance needs to be included on timing, methods, and audience. For instance, the following questions could benefit from additional guidance from FDA:

1. Would these engagements be considered formal or informal meeting requests and what information would a stakeholder need to provide in advance for the request to be granted?
2. Would there be a particular timeline that FDA could commit to granting the meeting or engagement?
3. Could this be facilitated by FDA's patient affairs staff or patient-focused drug development staff at FDA?

In NORD's experience preparing for the PKD patient-focused drug development meeting, FDA provided helpful feedback to avoid biasing patient input. NORD recognizes this could create additional burden for FDA staff, so it is important to manage stakeholder expectations by being as explicit as possible in outlining the parameters for engagement with FDA.

One very important aspect of this process that is not delineated in the Draft Guidance is what to do with the information once it has been obtained. In other words, how would the determinations of what is important to patients be transmitted to inform the development of COAs and patient preferences? We suggest FDA more clearly articulate how this valuable information can be shared with FDA, researchers, and drug developers. Perhaps a repository similar to FDA's patient-focused drug development webpage could be set up.

NORD also recommends that FDA provide guidance on best practices to ensure the return of information to the community that participated in the research. For example, through our "Voice of the Patient Report" on PKD, NORD will be providing patient and caregiver participants with a publicly available, comprehensive report on the information that was gathered during the meeting.

In terms of more specific suggestions for the Draft Guidance, NORD offers the following comments.

When discussing the background research in section II, in addition to literature reviews and consultation with relevant subject matter experts to develop research questions, NORD recommends that FDA amends the Draft Guidance to include a suggestion for the consultation of patients in the development of these questions. This early involvement would help when entities are then testing their questions before administering the survey.

In section III, FDA should discuss considerations in determining whether to record qualitative sessions and the potential implications. Such recordings could provide an important study resource for researchers. This could include interview transcripts to work from that capture detailed participant response data, including intonation. Limitations to consider, however, are that the transcription of recorded interviews may add time and require additional resources, may present a barrier for interviewers trying to establish rapport, and for participants to share their experiences openly.

NORD supports FDA's comment in section IV.B regarding the choice of survey administration mode. Survey instruments for screening and exit visits can help elicit feedback on patient experiences in a clinical trial. Moreover, it may be particularly useful to hear from patients who drop out early about why they dropped out, what challenges/barriers were faced, etc. This information may be important to inform the design of patient-focused trials. Natural history study platforms, such as NORD's IAMRARE, can support the collection of this data and allow for a variety of stakeholders to benefit from the information provided by patients.

NORD appreciates that FDA has included a dedicated section (Section VI) to address special populations, including patients with rare diseases. Many of the special considerations identified are consistent with considerations identified in other FDA drug development guidances, particularly those that focus on patient engagement and involvement in clinical trials. It is helpful to highlight these special considerations in the pre-development, pre-clinical trial phase too, as is done in this Draft Guidance. To enhance the utility of this section, NORD recommends expanding upon each of these considerations or cross-referencing this section with other guidances where these considerations are discussed in more detail.

In Appendix 4, the Draft Guidance implies, but does not explicitly state that having more than one qualitative coder is appropriate. NORD recommends that this guidance state the recommendation explicitly. Having more than one coder allows for calculations of intercoder agreement. Additionally, it is important to distinguish from the previous point that coding frameworks and analysis plans evolve as researchers work with qualitative data and that the process should be viewed as cyclical where each individual coder recodes the data at least two times. These approaches increase the consistency and reliability of the findings. We request that the FDA clarify the points on page 31, line 697 and page 33, line 741 to distinguish that: 1) individual coders should recode the data more than once; and 2) at least two coders should code the qualitative content using the same coding framework.

We also encourage FDA to consider adding the following limitations to the specified tables.

> Table 2, for in-person focus groups: a trend toward the mean with group dynamics may be observed so facilitators may end up hearing less from participants on the upper or lower extremes and in addition, participants may be influenced by others in the group resulting in a condensed range of perspectives or opinions.
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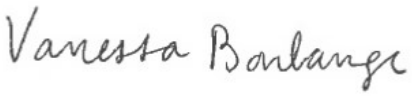
> Table 3, for open- and closed-ended questions: it is important to be thoughtful and intentional about determining the appropriateness of a N/A or "other" response option.

Table 3, for close-ended questions: with response options, it is important that the scale remains in the same order or that instructions explicitly note the change for participants to avoid erroneously capturing responses based on position in the scale rather than content.

Table 5, for Delphi panels: if threshold for consensus is not pre-defined it can result in a very lengthy process. For example, designing the study so that at the start of the delphi process the stakeholders and researchers have a shared understanding of the threshold, e.g. the point at which consensus will be defined, will allow consensus to be arrived at more efficiently and expeditiously.

NORD appreciates the opportunity to comment and looks 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 vboulanger@rarediseases.org or 203-304-7263.

Sincerely,



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