December 14, 2018

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

Re: Docket No. FDA-2018-N-2455-0001: Patient-Focused Drug Development Guidance: Methods To Identify What Is Important to Patients and Select, Develop, or Modify Fit-for-Purpose Clinical Outcome Assessments; Public Workshop; Request for Comments

Dear Sir or Madam:

On behalf of the 30 million Americans with one of the approximately 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) thanks the Food and Drug Administration (FDA) for the opportunity to provide comments on the Agency's "Patient-Focused Drug Development Guidance: Methods To Identify What Is Important to Patients and Select, Develop, or Modify Fit-for-Purpose Clinical Outcome Assessments; Public Workshop; Request for Comments."

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.

NORD has long supported patient involvement in the drug development and regulatory review process. 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 can offer these uniquely important perspectives.

Over the course of the last ten years, FDA, often under the instruction of Congress, and in consultation with patients and their representatives, has made great strides in ensuring the patient voice is integrated within the therapeutic development and review process. The Patient Focused Drug Development (PFDD) initiative created by the Food and Drug Administration Safety and Innovation Act (FDASIA) established a series of public meetings in which patients with specific diseases could offer their experiences and perspectives. We believe these meetings were highly successful, and we are already aware of positive outcomes that have resulted.

More recently, the 21st Century Cures Act and the Food and Drug Administration Reauthorization Act (FDARA) further advanced the incorporation of the patient voice in the therapeutic development process. October's public workshop, the first draft guidance in this

series, last year's December 18th workshop, the accompanying discussion document, and the additional upcoming draft guidances and public workshops all result from these two laws. We were pleased to help craft these legislative and regulatory proposals, and we are excited to participate within this exciting FDA initiative. The following comments reflect our feedback to FDA on the October 15 and 16 public workshop and the accompanying discussion documents. We will pay particular attention to the questions posed by FDA within these documents, and answer from the perspective of the rare disease patient. We hope these comments can be helpful as FDA crafts the second and third guidances on PFDD.

Overall we are pleased with the October workshop and accompanying discussion documents, and view these proceedings as a step forward for the initiative. Whereas we were somewhat concerned with previous documents within this initiative because they did not give enough guidance to the patient and patient organization community, and did not incorporate enough recognition and advice for overcoming the complexities rare diseases bring to these efforts, the latest public meeting and discussion documents improve on both of these areas.

There are still ways in which the documents could improve. For example, FDA could be much more emphatic on the importance of data generated from patients. On page 7 of the discussion document on clinical outcomes assessments (COA), FDA states that, "patient input can help inform benefit-risk assessments for regulatory decision making." Instead, patient input should form the basis of benefit-risk assessments for regulatory decision making as who has a better perspective on the benefits and risks of a product than the patients themselves.

The remainder of our comments on the document will be organized using the specific questions FDA poses in both documents. Below are our responses.

Guidance 2:

1. *Identify best practices (qualitative and quantitative methods) for eliciting information about what aspects of symptoms, impacts of disease, and other issues important to patients that are representative of the target population of patients and caregivers. What level of detail of the methodology do you think is appropriate for this guidance?*

   We have several suggested incorporations for the upcoming draft guidance based upon this discussion document. First, regarding best practices for eliciting qualitative information, semi-structured interviews are likely the best option within rare diseases. The flexibility and adaptability they provide can be especially valuable in rare diseases with minimal available natural history data.

   Second, we encourage FDA to put a stronger emphasis on selecting well-established questions that are already used in research, and are likely to continue to be used going forward. This will facilitate the ability to look at data across various studies to maximally leverage the information collected. We ask FDA to emphasize this benefit within the upcoming draft guidance.

Third, we believe FDA should offer additional advice and guidance on what level of methodological detail is advisable in different circumstances. Most rare disease patient organizations will be looking to FDA to advise them on what methodology makes the most sense for their specific efforts, and currently that advice and guidance is largely missing from this document. We hope FDA will include further direction in the upcoming draft guidance.

2. *What sample size will elicit sufficient information about the patient experience to assure representativeness but is feasible?*

   Inadequate sample sizes are an inherent problem within rare diseases, and have helped spur plenty of statistical and methodological innovations within clinical trials. Much of this innovation has been encouraged, if not led, by FDA. We would hope that, once again, FDA will provide our community with guidance on how to overcome inherent sample size issues within rare disease patient populations.

3. *What other data (e.g., data from social networks, accelerometry, room surveillance) can be used to elicit or derive information about the patient experience in a feasible manner?*

   First, we join other attendees from the workshop in asking FDA to clarify the term "room surveillance." As it is currently phrased, this activity could be perceived as troublingly invasive.

   Second, as FDA is considering additional methods of collecting data to include within the draft guidance, we ask that it remain mindful of several considerations. We encourage FDA to consider the burden the collection method will pose on the patient. Passive methods, such as an accelerometer, are much less burdensome on patients, especially those who are experience symptoms that make activity difficult.

   We also encourage FDA to consider the ability of the collection method to generate data that can be integrated with data collected from other sources. Finally, we encourage FDA to emphasize support for creative data collection methods within rare diseases. Innovation may be the key to unlocking new ways to collect data from rare disease patients.

4. *Use of social media is recognized as a potential data collection method to elicit information regarding patient experience.*
   a. *Will information collected from social media sources meet the goals of Guidance 2 (e.g., collecting representative information on important symptoms, burdens, and related issues)? If yes, how do we determine the adequacy of data from social media sources?*

      We are pleased that data collected from social media is being considered by FDA for Guidance 2, and we encourage FDA to move forward with this inclusion. We also concur with the advantages and disadvantages listed within Table 6 in Appendix 7.

Furthermore, we concur that data collected from social media has its drawbacks. However, individuals with rare diseases often have no other recourse to gather and communicate with one another outside of social media due to the isolated nature of their disease. Consequently, we encourage FDA to ensure social media options for data collection are included as they may be particularly beneficial for those with rare diseases.

b. Is there a need for patient verification if social media is the data collection method to elicit information about the patient experience?

Given the inherently small populations within rare diseases, it may be particularly important to ensure every participant is actually a patient, or at least meets whatever qualification the study requires. Only a handful of unqualified responses could skew the entire study within rare diseases whereas they may not be nearly as damaging within common diseases.

With this said, verification techniques may be disincentivizing for some within the community, particularly if the individual is hesitant to publicly identify themselves as a patient. This happens often within rare diseases as stigma, discrimination, and other harmful occurrences have historically resulted from individuals publicly identifying themselves. Security of their protected health information will be critical to encouraging study participation.

5. *Important considerations are needed for special populations, such as pediatrics, the cognitively impaired, and rare diseases. What other special populations (beyond pediatric, cognitively impaired, and rare diseases) should be identified for this FDA Guidance? Are there any other factors to consider when eliciting information from special populations?*

We thank FDA for acknowledging the need for further considerations around collecting data from individuals with rare diseases. This recognition, and hopefully ensuing information within the upcoming draft guidance, will greatly facilitate this data collection. Section 3 of Appendix 2 includes incredibly important special considerations for rare disease patients, and we thank FDA for their inclusion.

With this in mind, we recommend that FDA expand section 3 of Appendix 2 to include further considerations for collecting data from rare disease patient populations. These include, but are not limited to:

a. There is a general lack of natural history data available for rare disease patient populations. This makes it difficult to define target patient populations, and design or select appropriate questions for the patient community
b. As referenced earlier, there are special considerations warranted for the protected health information (PHI) of those in the rare disease community. Given the extremely low prevalence of many rare diseases, seemingly anonymous data can actually be identifying, such as initials, zip codes, and

genotypic information. In addition, patients with rare diseases have historically been discriminated against, so security precautions must be particularly vigilant.

c. Once again, additional information on how to appropriately sample from rare disease patient populations is needed. Not only are some populations too small to employ classic empirical methods, many rare disease patient populations include many subpopulations that are also too small employ traditional methodology. We request FDA to include additional information in Guidance 2 on how to appropriately sample within rare disease patient populations, as well as what additional statistical precautions are warranted.

6. *The level of rigor needed for generating patient experience data can vary across studies and will depend on the intended use. However, there are certain elements common to all studies such as a protocol, structured data collection, and analysis. How much detail about each aspect would be useful in guidance? On a website? Elsewhere?*

   We will once again reiterate the importance of FDA being as thorough as possible in its assistance to the rare disease community as the community collects data. Patient organizations in the rare disease community are generally quite small and under-resourced, and do not have the time and expertise to devote to extensive, complex, and robust data collection.

   While Guidance 2 is a logical location for such instruction, an easy-to-use website with readily accessible FDA experts prepared to answer questions may be ideal. In addition, pro-active educational offerings, such as webinars, meetings, and conferences, would also be beneficial to the community. Finally, a road map with branching logic that assists patient organizations through decisions involved with collecting data could be particularly beneficial.

7. *What document structure and content would be most useful for this guidance?*

   First, we would suggest that FDA include case examples of successful data collection methods, particularly in rare disease populations. These case studies can help instruct patient organizations on best practices, and what FDA views as successful.

   Second, FDA should consider including a decision tree in Guidance 2 to assist patient organizations with their decision making. This will help direct patient organizations towards the best data collection method for their particular community and their particular needs.

   Finally, FDA should consider expanding the glossary to include additional terms (such as room surveillance) that could engender confusion.

8. *Many potential research methods are available and not all could be included in the discussion document. Is it clear the Agency is open to discussion of the methods*

described and other methods, both within medical product programs and in the pre competitive space?

While it is clear the agency is open to other research methods, additional encouragement would be helpful in order to motivate stakeholders to look for new and innovative methods for collecting patient data.

In addition, FDA should offer additional guidance for how best to propose alternative data collection methods to FDA, and cite past studies of previously successful stakeholder groups that approached FDA with alternative methods.

9. *What are the most important timepoints when FDA input could be maximally helpful?*

Other than "early and often", we do not have any further advice to offer.

Guidance 3:

1. *Does the Roadmap Diagram (Figure 3) in the Guidance 3 discussion document capture the appropriate elements to strategize for the selection and/or development of a COA for use in clinical trials? If not, what are other factors that should be considered and where should they be positioned in the diagram?*

We have several comments to offer in response to the Roadmap Diagram offered. First, within the "Natural history of the disease or condition" subcategory of "Understanding the Disease or Condition", it is important to capture the amount of time it took to obtain a diagnosis as well as the type of clinician who is making the diagnosis, especially in rare diseases. This will instruct FDA on whether or not the time to diagnosis is being delayed because patients are not being seen by the appropriate healthcare provider, patients do not have access to healthcare and/or health insurance, or additional factors that could affect the patient's time to diagnosis.

Within the "Conceptualizing Clinical Benefit" category, it is important to recognize one patient's "meaningful clinical benefit" may differ substantially from another's.

Finally, under the "Selecting/Developing/Modifying the Outcome Measure" category, FDA should clarify whether or multiple COAs could be selected and potentially even combined in order to present a more holistic understanding of the patient experience. Other factors to consider under this category pertaining to COAs is whether or not the COA is appropriate for the intended patients (for example, age appropriate), and whether or not the patients actually played a role in choosing or developing the COA. Ensuring the COA is inclusive and covers multinational, multicultural, and multiregional populations is also valuable.

2. *Does the decision tree diagram (Figure 6) in the Guidance 3 discussion document capture the process to select, develop, or modify a COA sufficiently? If not, what are other factors that should be considered in this process and where should they be*

positioned in the diagram? Should this diagram replace the "Wheel and Spokes" diagram in the current PRO Guidance (Figure 3 in FDA PRO Guidance)?

The decision tree diagram is precisely the kind of diagram that we believe can be most helpful to the rare disease community when making decisions on COAs, and we thank FDA for this approach. FDA should ensure the decision tree is flexible, and allows for COAs to be modified as the study progresses. This can be particularly important within rare diseases where little is known, and the study needs to modified as more is learned.

3. *Important considerations are needed for special populations, such as pediatric, the cognitively impaired, rare diseases, and patients from different language and cultural groups. Does the Guidance 3 discussion document capture all the relevant special populations? What other populations should be identified for this FDA Guidance? Are there any other factors to consider when selecting, developing, and implementing COAs for these populations?*

First, we strongly agree with FDA's suggestion that, "sponsors should conduct well-designed natural history studies independently or through partnerships with patient organizations and/or utilize existing natural history and /or patient registry data." We ask that FDA place special emphasis on sponsors partnering with patient organizations to conduct such studies in order to ensure the data and data collection are patient-focused, and the data may be used and employed by the patient organization in multiple settings, rather than proprietarily held by the company.

NORD's IAMRARE™ natural history data registries aim for precisely this goal. NORD partners with patient organizations to run rare disease registries, and we are fully prepared to assist FDA in collecting this data through our IAMRARE™ Registry Platform. We provide general research guidance, project management and IRB services, technical support, and opportunities for organization-to-organization mentorship. NORD requires that each patient organization have a Scientific Advisory Board to advise on the development of survey questions, the longitudinal measurement schedule, and other disease-specific aspects of the research development.

In order to facilitate the collection of these important data, we reiterate a request from our September 11, 2018 comments to FDA on your "Draft Guidance for Industry Patient-Focused Drug Development Collecting Comprehensive and Representative Input." Guidance from the FDA about sound research approaches and best practices for the rare disease community, in addition to guidance on a standard set of (rare disease) research questions and also high-value data elements that the FDA could then use to inform decisions would be incredibly meaningful. Of course this information can vary to some degree from disease to disease, or population to population, but any further guidance from FDA would be helpful. This guidance would allow rare disease patient organizations to develop a bi-directional pipeline for data sharing and capture in a way that reflects the priorities of the FDA in addition to the needs and experiences of the community.

Second, we concur with many of FDA's assertions within this section, including FDA's suggestion to choose endpoints that are relevant to the most number of patients within that population while still collecting data on endpoints that may only be relevant to portions of the community, as well as the recommendation for sponsors to interact with the patient community early and often. This latter point cannot be emphasized enough, and we strongly encourage FDA to strongly encourage sponsors to partner and collaborate with patient organizations from the outset.

a. What other factors need to be considered when determining a reasonable minimum age to self-report in a reliable and valid manner?

Additional factors that could be considered when determining a reasonable minimum age to self-report include measures of maturity, tests for whether or not the child can complete tasks independent of a guardian, and other ways in which reliability and validity of a child's answers can be ascertained.

Furthermore, many, if not most, children with rare diseases have had the disease all their lives, and may have difficulty in explaining their symptoms as they have never experienced any other way of life. The questions with the COA must take into account this possibility, and be structured in a way that still captures valid and reliable data.

These suggestions are particularly important as it is estimated that half of all individuals with a rare disease are children, and their perspectives on their rare disease cannot be disregarded.

b. What other factors need to be considered when determining a reasonable minimum level of cognitive function to self-report?

As FDA recognizes, many rare diseases feature cognitive symptoms that may hinder data collection. This is why the COA must be developed in such a way that it is applicable to various cognitive functioning levels in order to not skew the results towards those with stronger cognitive abilities

c. How to address selection of COAs for people who move between a self-report status and inability to self-report?

In order to facilitate accurate continued data collection, collecting caregiver or familial data in addition to patient data in order to avoid or minimize gaps in the data could prove beneficial. These data can then be compared with each other while the patient is moving between self-reporting and the inability to self-report.

d. What are other factors and/or approaches to consider when using COAs in multinational, multicultural, and/or multiregional studies?

It is important to be sensitive to the differences across populations and create COAs that are inclusive and use terminology that can apply to various nationalities, cultures, and regions. In addition to these three variables, it is important to also craft COAs that account for differences in socio-economic status, sexual orientation, and other population differences that could result in different interpretations and abilities to participate within COAs.

e. Does the Guidance 3 discussion document appropriately present the important considerations for selection, development, and/or modification of COAs in rare diseases in sufficient detail and in a feasible manner? If not, what are other factors and/or approaches to consider?

We are very pleased that FDA has included a section specifically on considerations for COAs in rare diseases. Overall, FDA provides an excellent overview for what sponsors should consider when developing COAs for rare diseases. We have a few suggestions for further improvements in addition to the improvements offered above.

FDA should better define what meaningful outcomes might look like in rare disease populations taking into account that there will be far fewer participants within the COAs. Are there minimum thresholds for the number of patients that must participate in order for the data to be considered meaningful? What other special considerations will be taken into account when looking at data from the rare disease community?

In addition, does FDA have any advice on strategies to overcome the various special difficulties and limitations that are present in rare diseases? Finally, what special accommodations will FDA encourage, or at least consider, when developing COAs for rare communities that require additional assistance (such as visual or auditory aids, speech to text functions, and more)?

4. *Does the Guidance 3 discussion document capture the most appropriate and feasible methods to determine within-patient meaningful score changes in COA instruments? Are there any other methods to consider?*

We encourage FDA to ensure that the meaningful score change is flexible enough to account for changes or advances in medicine, as well as what the researcher and (most importantly) the patient deem to be meaningful. When developing COAs, it cannot only be what sponsors and FDA deem meaningful, and must instead include a variety of viewpoints.

5. *Are there recommendations for any changes to the definitions we include for the categories of COAs (PRO, ObsRO, ClinRO, PerfO)? Are any additional categories of COAs recommended?*

a. *Digital monitoring sensors can be used for clinical outcome assessment (e.g., step counts collected via actigraphy). Please suggest approaches or methods to provide evidence of fitness for purpose (content validity, construct validity, reliability, ability to detect change) for these tools. For example, walking speed rather than step count may be most relevant and meaningful to a particular patient population.*

   Additional considerations for digital monitoring sensors should include whether or not the design of the device facilitates accurate data collection across age groups, genders, ethnicities, and more. In addition, COA developers should ensure the data output from the device represents meaningful data to the patient, and not just easily-collected data that has little meaning to the patient's wellbeing.

   In addition, FDA and sponsors should be discouraged from employing digital monitoring sensors that could pose an undue burden on the patients wearing them. For example, if walking is necessary to collect data through the wearable, the sponsor should ensure this walking is not burdensome or harmful to the patient.

   Digital tools should be paired with PROs to ensure that not only the data collected by the digital monitoring sensors are meaningful to patients, but the collection of that data will not be burdensome to the patients.

6. *FDA strives to maintain flexibility in our evaluation of evidence, taking into account feasibility and practicality. Does the discussion document appropriately describe how FDA will assess whether a COA is fit for purpose?*

   We feel this discussion document appropriately describes how FDA will assess whether a COA is fit for purpose, and have no further comments.

7. *Does the discussion document present information about best practices for COA selection, development, and/or modification in a manner that can reasonably and rigorously be implemented in medical product development?*

   While this document is targeted for sponsors developing medical products, it may be useful to groups such as rare disease patient organizations that conduct natural history studies. A more robust description of best practices in the guidance may be a good resource for these organizations to better align their studies to have a complementary data set for clinical trials. FDA could include in Guidance 3 that sponsors and affiliated staff should be trained in explaining a study to participants as well as how to complete the COA.

8. *Is the audience described for Guidance 3 appropriate? If not, what are recommended changes?*

We believe the audience described is indeed appropriate, particularly since most developers of COAs will likely be industry. However, as stated many times before, it will be critical that patients are involved throughout the development and implementation of the COA.

9. *How do the good measurement principles presented in this discussion document apply to PerfOs and ClinROs, and what other evidence is needed?*
    a. *There is existing literature related to PerfOs and ClinROs (e.g., PerfO White Paper6 and ISPOR Task Force ClinRO paper7). Which principles from existing literature or other sources are important and appropriate for inclusion in FDA guidance?*

        We do not have additional comments in response to this question.

To conclude**,** we thank FDA for the opportunity to comment and we look forward to working with FDA to ensure rare disease patients and patient advocacy organizations are able to fully participate within this exciting initiative. For questions regarding NORD or the above comments, please contact Paul Melmeyer, Director of Federal Policy, at pmelmeyer@rarediseases.org, or 202-545-3828.

Thank you in advance for your consideration.

Sincerely,

Peter Saltonstall
President and CEO