



May 24, 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-0481: Rare Diseases: Natural History Studies for Drug Development Guidance for Industry

Dear Sir or Madam:

On behalf of the 25 to 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Disorders (NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the draft guidance entitled “Rare Diseases: Natural History Studies for Drug Development, Guidance for Industry” (Draft Guidance).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.

In 2014, NORD launched a rare disease natural history patient registry 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 thirty-six 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 1) to support drug development by characterizing and fostering increased understanding of the natural progression of rare diseases and the corresponding burden on patients; 2) to act as a resource for patient cohorts for clinical trials; 3) to support pre- and post-market surveillance; and 4) to foster development of clinical outcome assessments (COAs).

NORD is pleased to support FDA’s efforts to integrate the natural history of a rare disease into drug development and approval processes. The Draft Guidance demonstrates FDA’s clear understanding of the importance of natural history studies of rare diseases in identifying patient populations, developing clinical outcomes assessments and biomarkers, and in the design of externally controlled studies. The Draft Guidance is a clear roadmap for industry to successfully capture natural history data that can support drug development and approvals. Below are our specific comments and recommendations for strengthening the Draft Guidance and for developing further guidance.

NORD applauds FDA for acknowledging and understanding the importance of patient organizations in the rare disease research space, with respect to natural history studies. The Draft Guidance draws attention to the importance of patient organizations in the initial recruitment of study participants. The document also addresses the need for study retention assistance by stating: “Patients’ continuing study participation ensures the robustness of follow-up data. Patient advocacy or support groups can make an important contribution in keeping the patient community interested and engaged and in providing valuable perspectives both on minimizing burdens to patients and families and on the acceptability of proposed investigations.” (Draft Guidance at 13).

The Draft Guidance demonstrates FDA’s understanding of the critical role played by patient organizations as an extremely valuable resource because of their existing relationships with rare disease patient communities. These relationships have the potential to maximize natural history study participation and strengthen the power of the data produced.

NORD believes the Draft Guidance could be strengthened in this regard by further explaining the ways in which patient groups can partner with drug developers on natural history studies. In an earlier guidance document, FDA has previously suggested 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.”¹ NORD reiterates our comments on that guidance urging FDA to expand this concept and specify the value of sponsors partnering with patient organizations to coordinate the natural history studies.² Partnering with community organizations ensures that the data and data collection processes remain patient-focused. It will also enable the data to be used and employed by the patient organization in multiple settings, instead of being proprietarily held by an industry partner.

Multi-stakeholder partnerships offer an enhanced ability to collect and utilize real-world evidence (RWE) for rare diseases that did not exist prior to natural history study implementation. The Draft Guidance states that natural history studies may “uncover sentinel events or detectable physiologic changes that are important predictors of disease progression or that are clinically important in their own right.” (Draft Guidance, pg. 3) This RWE is highly beneficial for drug development and approval. The Center for Drug Evaluation and Research (CDER) Director Janet

¹ FDA, “Patient-Focused Drug Development Guidance Public Workshop: Methods to Identify What Is Important to Patients and Select, Develop, or Modify Fit-for-Purpose Clinical Outcome Assessments; Workshop Date: October 15-16-2018,” at page 31 (online at: <https://www.fda.gov/media/116277/download>).

² NORD, Comments on “Patient-Focused Drug Development Guidance Public Workshop: Methods to Identify What Is Important to Patients and Select, Develop, or Modify Fit-for-Purpose Clinical Outcome Assessments; Workshop Date: October 15-16-2018,” Docket No.: FDA-2018-N-2455-0001 (December 14, 2018).

Woodcock has previously stated that RWE can help "answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval."³

NORD notes that these understudied populations could reflect sub-types of a condition or variable rates of disease progression (rapid, chronic, or slow) within rare disease communities. NORD is fully prepared to assist FDA in collecting this de-identified natural history data through our platform in order to analyze and understand heterogeneity within the patient population. In addition, NORD's platform includes a harmonized core survey set that allows for cross-disease analysis to assess commonalities across conditions. This data could suggest new populations where a drug may work or even highlight patient groups that are using a drug off-label for symptom management.

NORD believes that patient data should be kept in the hands of the community. Our platform allows patient community organizations to own their data and to partner with relevant stakeholders as they deem fit. In 2018, the IAMRARE™ registry platform launched a new multi-stakeholder model in partnership with The Foundation for Prader-Willi Research and Zafgen Inc. The model permits industry and researchers to conduct embedded sub-studies in parallel with the main natural history study. This allows study sponsors to conduct time-bound or funding-bound research studies that target the specific data needs of each partner, thereby reducing the need for redundant registries, allowing patient populations to remain intact on a centralized platform and decreasing participant burden in research.

NORD suggests that FDA should clarify the Draft Guidance to better explain the importance of barriers and facilitators within rare disease research. NORD strongly supports intentional study designs that reflect representative study populations, and we restate a request from our earlier comments on another guidance document that FDA assist in the collection of these essential data.⁴ NORD believes that further guidance from FDA regarding inclusive recruitment, retention, and engagement best practices for the rare disease community would be valuable in order to ensure that research study designs reflect a representative population and that disease knowledge, diagnostics, therapies, and other research outputs are broadly available, accessible, and applicable.

In addition, guidance on a standard core set of rare disease research questions and high-utility data elements, in addition to the use of international data standards, terminologies and clinical outcome assessments, would help researchers capture high-value data to inform and support FDA decision-making.

NORD strongly agrees with FDA's advice regarding the importance of thoughtful study protocols, the incorporation of common data elements, and dissemination and analysis planning when designing natural history studies. NORD's IAMRARE program provides registry clients with general research guidance, project management and IRB services, human subjects research training, technical support, and opportunities for organization-to-organization mentorship. A

³ FDA, "Framework for FDA's Real-World Evidence Program," at 13 (2019).

⁴ NORD, Comments on "Draft Guidance for Industry Patient-Focused Drug Development Collecting Comprehensive and Representative Input" (September 11, 2018).

Scientific Advisory Board advises patient organizations on the informed consent, development of survey questions, the longitudinal measurement schedule, and other disease-specific aspects of the research design.

Overall, NORD agrees that natural history studies are vital to research and drug development in the rare disease space. Natural history studies have the ability to aid in the identification of patient populations, the development of clinical outcomes assessments, biomarkers, and endpoints, as well as the design of and mechanism for externally controlled studies. NORD is pleased that FDA noted additional benefits such as establishing new communication pathways for rare disease communities, identifying specialty care centers and methods to improve patient care. NORD's IAMRARE™ registry platform aims to achieve all of these goals to accelerate progress for the rare disease community.

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 in high-quality, high-impact research. For questions regarding NORD or the above comments, please contact me at rsher@rarediseases.org, or 202-545-3970. Thank you in advance for your consideration.

Sincerely,

/s/ Rachel Sher

Rachel Sher
Vice President of Policy and Regulatory Affairs