February 5, 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-2018-N-4000: Framework for a Real-World Evidence Program; 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 or Agency) for the opportunity to provide comments on the Framework for FDA's Real-World Evidence Program (Framework).

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 worked closely with Congress and the Agency on the drafting and enactment of section 3022 of the 21st Century Cures Act (Cures Act, Public Law 114–255), which not only authorized FDA's Patient-Focused Drug Development (PFDD) Initiative, but also enacted new requirements on real-world evidence (RWE) in new section 505F of the Federal Food, Drug and Cosmetic Act (FFDCA). The law required FDA to publish the Framework, after convening a public meeting and consulting with patients and other stakeholders, to facilitate and accelerate utilization of RWE for the development of new drugs and biological products and to better assure their post-market safety.

Overall we are very supportive of FDA's revised framework and its continued dedication to using RWE to support clinical decision making and drug development for the rare disease community. In particular, we believe NORD's IAMRARE Registry Program could play a critical role in ensuring RWE and real world data (RWD) is appropriately and expediently collected. Below are our comments on specifically how FDA can incorporate registries, such as NORD's, in these efforts.

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**Implementation of the Framework Must Leverage Rare Disease Registries and Reflect Patient Perspectives:**

NORD believes that the Framework is an important foundation for expanded and improved generation and utilization of RWE to support the Agency's regulatory decision-making, premarket reviews, and assuring post-market safety of drugs and devices to diagnose and treat rare disorders. Historically, the FDA has worked diligently to anchor their work around the patient, meaningfully incorporating patient perspectives into the drug approval process and creating a network to educate and involve patients more effectively in regulatory decisions.

Consistent with its statutory mission and these policies, the Agency should take specific steps as it implements the Framework to utilize and leverage existing sources of RWE for rare disease patient populations, such as the IAMRARE™ Registry Program, and sustain its engagement and collaborations with patient organizations to assure that patient perspectives continue to be central to the expansion of RWE into the drug development and regulatory review processes.

*Patient Registries, such as the IAMRARE™ Registry Program are a Critical Source of RWE:*

The Framework appropriately emphasizes that "[p]atient registries are [a] source of RWD that could be used to generate RWE" (Framework, pg 17). In order to facilitate the development of treatments for rare diseases and support the generation of RWE, NORD has created the IAMRARE™ Registry Program, a Natural Histories Patient Registry Platform, with extensive input from FDA, the National Institutes of Health (NIH), patients, organizations, and experts in the field.

NORD's platform is an easy to use system that allows patients and organizations to inform and shape medical research and translational science for rare diseases by launching high-quality, customized registries to collect the data needed to define the natural progression of their disease – ultimately advancing product development.

With reference to RWE, the Agency notes that registries' "fitness for use in generating RWE requires sufficient processes, such as those to gather follow-up information when needed, to ensure data quality, and to minimize missing or incomplete data." (id.) NORD partners with patient organizations on the development of disease-specific longitudinal, natural history studies. NORD provides a common data collection infrastructure across conditions that gathers both common cross-disease survey data in addition to disease-specific survey data. The platform has the ability to capture longitudinal data on a set schedule while also allowing for ad hoc real-time data capture through surveys designated to accept updates.

In addition, the IAMRARE platform collects related electronic medical record information via an upload feature, where participants can share lab results, genetic testing, images, and clinical medical record data. NORD also provides best practice guidance and templates for emails, social media, and legal agreements (consent, data sharing) for patient organizations to engage with their patient populations. Rare diseases present unique challenges for researchers and companies working towards treatments and cures.

The Framework notes that electronic health records (EHRs) and claims data "may not capture all data elements needed to answer the question of interest" and that "[e]ven when captured, the way the data elements are captured in the EHR may limit their accessibility" (Framework, p. 17). NORD concurs and encourages the Agency to further explore and rely upon patient registries as they are more consistent and reliable sources of patient experience data in standardized formats. It will be important for FDA to collaborate with patient organizations, as well as academic and industry investigators to rely increasingly upon patient registries as sources of RWD which can draw upon relevant EHR data where necessary for data validation or event-based reporting.

The IAMRARE registry program can also enable the "pragmatic and hybrid clinical trials, including decentralized trials that are conducted at the point of care – and that incorporate real world evidence (RWE)" that Commissioner Gottlieb cited as recently as January 28 as means to increase efficient clinical investigations, reduce administrative burdens, and most importantly, "allow patients to receive treatments from community providers without compromising the quality of the trial or the integrity of the data that's being collected."

As the Framework quotes Center for Drug Evaluation and Research (CDER) Director Janet Woodcock, 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." (pg. 13) In the case of rare disorders, NORD notes that such populations could reflect sub-types of a condition or rates of disease progression (rapid, chronic, or slow) for which data could be captured through patient registries. Moreover, cross-disease analysis for commonalities across conditions could also suggest new populations where a drug may work or bring to light populations that are using a drug off-label.

*Use of RWE Will Facilitate Implementation of Other FDA Initiatives to Expedite Innovative Drug Development.*

NORD believes that FDA's recently updated rare disease development draft guidance underscores the importance of registries like IAMRARE to the feasibility, design, and initiation of natural history studies. (FDA, Rare Diseases: Common Issues in Drug Development Guidance for Industry, February 2019) Patient registries can mitigate structural concerns with RWE data gathered through observational study designs and the ability to reach causal inferences from such data.

Registries such as IAMRARE can capture data from an entire rare disease community, across many diseases and conditions, providing robust and reliable sources of baseline data, indices of existing evidence for the natural history of a given rare disease or condition, and the ability to look across conditions for commonalities. The data collected has the ability to inform and transform patient care, unite patient groups, and provide an understanding of how specific diseases are expressed over time. Longitudinal patient-reported, patient-experience data can also contribute to a more robust knowledge-base for the evaluation of individual and global economic burden of disease and inform therapeutic development for the rare disease community.

As an example of how patient registries can serve as a platform for collecting natural history data across platform trials, and potentially even serving as a historical control, we refer to the 2016

cooperative agreement between the Agency and NORD to develop natural history studies with twenty rare disease patient groups through NORD's Natural History Study research platform. The agreement enabled the collection of disease-specific longitudinal, natural history information from individuals diagnosed with selected rare diseases. Examples of core data elements that are measured within and across each registry at NORD include patient-reported, patient experience outcomes related to diagnosis and treatment, quality of life, management of care, clinical testing samples, and clinical reporting.

Additionally, NORD believes that the patient registries cited in the Framework could serve as effective platforms for the clinical investigators and potential sponsors cited in Commissioner Gottlieb's and Center for Biologics Evaluation and Research (CBER) Director Peter Marks' January 15 statement, committing to issue guidance on cellular and gene therapy "outlin[ing] a proposed innovative trial design by which individual researchers can pool their clinical data after following a common manufacturing protocol, and thereby develop a more robust data set for purposes of gaining a BLA". Flexible acceptance by FDA and creative use of mechanisms for RWE such as patient registries could facilitate uptake of such novel pathways to premarket submissions.

*Use of RWE for Drug Development Must Be of Equal Priority to Assuring Post-Market Safety in Implementing the Framework.*

NORD also encourages FDA to pursue broad, expedient, and transparent implementation of the Framework, and support and accept RWE in premarket reviews for novel as well as previously approved treatments. The FDA has made historic use of RWD for purposes of pharmacovigilance and post-market safety, not only through passive, voluntary reporting systems such as MedWatch but also through active surveillance systems like the Sentinel Initiative.

As Commissioner Gottlieb noted on December 6, "RWD and RWE can be especially useful for post-market monitoring of the safety of products during their use in real world settings." NORD applauds the Agency's emphasis in the Framework on discussing and providing guidance on the use of RWE to support drug and device development, consistent with congressional intent.

NORD emphasizes that FDA's implementation of the Framework must expand upon the "limited instances [where] FDA has accepted RWE to support drug product approvals, primarily in the setting of oncology and rare diseases". (Framework, pg. 9) While the Cures Act focuses upon use of RWE "to support the approval of a new indication" for previously approved drugs or biological products, we encourage the FDA to not only support new indications of use of approved therapies, but to explore the use of RWE as an additional source of data to support and encourage drug development programs for new molecular entities (NMEs) and previously unapproved products. FDA's guidance on trial designs, sources of evidence, data validation and other critical issues in generating and relying upon RWE could assist patients, investigators, and sponsors with their rare disease development programs regardless of whether the candidate molecule has been approved before or not.

The substantial unmet medical needs of patients with rare disorders militates strongly for this more expansive approach to RWE. There are an estimated 7,000 rare diseases, which are

defined as a disease affecting 200,000 or fewer people. Today, over 90 percent of rare diseases still have no treatment (the approximately 500 approved orphan products treat nearly 600 rare diseases). The barriers and significant obstacles that hinder the pursuit of rare disease therapies can be lessened by the FDA's support for the development of RWE in rare diseases.

This unmet need also underscores the importance of FDA moving forward with the usage of RWE in an expedient and transparent manner. Similar to FDA's PFDD Initiative, the Agency could publish resources and timelines on its website in order to bring predictability and opportunities for participation to the rare disease patient community.

**Implementation of the Framework Can Only Succeed Through Sustained, Constructive Engagement with Patients.**

NORD is pleased that the Framework emphasizes that "[s]takeholder engagement has been, and will continue to be, an important part of FDA's RWE Program." (Framework, pg. 26) We encourage FDA to create, enter into, rely, and leverage public-private partnerships and demonstration projects, building on its work with patient groups such as NORD, as well as organizations such as the Duke Margolis Center for Health Policy and the National Academies of Sciences, Engineering, and Medicine.

NORD would also be willing and available to assist the Agency on adapting standards or developing new standards "to maximize the utility of RWD and ... [identify] relevant standards and methodologies for collection and analysis of RWD." (Framework, pg. 14) We believe our registry platform could provide an avenue to test and validate new standards to ensure that they are fit-for-purpose across rare conditions.

We thank the Agency for the opportunity to comment, and look forward to working with FDA on implementation of the Framework to facilitate the development of new medicines and new uses of existing therapies, to better ensure their safety in actual clinical use, and 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 me at rsher@rarediseases.org, or 202-588-5700.

Thank you in advance for your consideration of these comments.

Sincerely,

Rachel Sher
Vice President of Regulatory and Government Affairs