December 17, 2024

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U.S. Food and Drug Administration
10001 New Hampshire Ave
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Peter Marks, M.D.
Director, Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave
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Re: Docket No. FDA-2024-D-2052 for "Integrated Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice"

Dear Dr. Cavazzoni and Dr. Marks:

On behalf of the more than 30 million Americans living with one of the over 10,000 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(NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance "Integrated Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice."

NORD is a unique federation of non-profits and health organizations dedicated to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD was founded 41 years ago, after the passage of the Orphan Drug Act (ODA), to formalize the coalition of patient advocacy groups that were instrumental in passing this landmark law. Since that time, NORD has been advancing rare disease research and funding to support the development of effective treatments and cures; raising awareness and addressing key knowledge gaps; and advocating for policies that support the availability of and access to safe and effective therapies.

An estimated 95% of the more than 10,000 known rare diseases do not yet have an FDA-approved treatment, making innovative and diverse approaches to rare disease research and drug development critically important, since conducting traditional randomized, double-blind, placebo-controlled trials in rare diseases can be challenging. Rare disease patients frequently need to travel long distances to participate in trials, facing financial barriers that can negatively impact recruitment, retention, and diversity. These challenges disproportionately affect patients from historically underserved communities, making it harder to ensure representative trial populations. As rare diseases can manifest differently in each individual, these obstacles further widen the knowledge gaps, particularly in understanding how they affect diverse populations.[1]

Integrating clinical research into routine clinical care holds promise to better serve the rare disease patient population. NORD notes that this draft guidance is consistent with Commissioner

[1] U.S. Department of Health and Human Services. (2023, April 24). *Diversity and inclusion in clinical trials*. National Institute of Minority Health and Health Disparities. https://www.nimhd.nih.gov/resources/understanding-health-disparities/diversity-and-inclusion-in-clinical-trials.html#:~:text=People%20may%20experience%20the%20same,can%20benefit%20from%20scientific%20advances.

Califf's longstanding call[2] for increased reliance on clinical care for evidence generation and believes application of the guidance will help drug sponsors effectively integrate randomized controlled trials (RCTs) into routine clinical practice. NORD also appreciates that the draft guidance is the latest in FDA's real-world evidence (RWE) efforts to improve the application of RWE methods in evidence generation, which is of importance to rare disease drug development.[3] However, NORD offers the specific recommendations below for how to maximize the impact of this draft guidance to help address challenges in drug development faced by the rare disease community.

Recommendation 1: Provide more specific guidance on the use of point of care trial designs for rare diseases.

To augment the scope of this guidance, NORD urges the Agency to elaborate on the potential application of point of care trials for rare diseases. As noted, such trials include simple studies that utilize large patient populations to assess the effect of simple interventions or potential new uses of approved drugs. While repurposing is an important strategy for rare disease drug development, the guidance should build on increased coordination between rare disease clinical centers, which embodies the FDA's observation that "[l]everaging established health care institutions and existing clinical expertise in the medical community can reduce startup times and speed up enrollment." In short, additional guidance on how rare disease clinical networks can organize point of care trials for small patient populations would be important for successful implementation. (see *infra,* Recommendation 4)

NORD also appreciates that the draft guidance recognizes facilitating trials as part of routine clinical care could improve patient access to and participation in clinical trials especially amongst historically under-represented populations, and enhance the collection of post-market data and potential repurposing data. Rare patients may see up to five physicians and experience delays of five to seven years before receiving an accurate diagnosis for their condition,[4] often encountering geographical obstacles to care.[5] FDA should consequently add language and guidelines specific to rare diseases, particularly in applying a quality by design (QbD) approach in trials integrated into routine clinical care.

Integrating trials into routine clinical practice allows for the collection of real-world evidence – of potential value for rare diseases when trial data is sparse – and could also accelerate the evaluation and validation of biomarkers used to support critical decisions, such as for patient

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[2] R. Califf. Now is the time to fix the evidence generation system. Clinical Trials. 2023;20(1):174077452211476. doi:https://doi.org/10.1177/17407745221147689

[3] FDA, Framework for Real-World Evidence Program, December 2018, at https://www.fda.gov/media/120060/download?attachment; FDA, Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products, December 2023, at https://www.fda.gov/media/154449/download; FDA, Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, February 2023, at https://www.fda.gov/media/164960/download.

[4] Zhang Z. Diagnosing rare diseases and mental well-being: a family's story. Orphanet J Rare Dis. 2023 Mar 6;18(1):45. doi: 10.1186/s13023-023-02648-y. PMID: 36879253; PMCID: PMC9990187.

[5] Willmen T, Willmen L, Pankow A, Ronicke S, Gabriel H, Wagner AD. Rare diseases: why is a rapid referral to an expert center so important? BMC Health Serv Res. 2023 Aug 23;23(1):904. doi: 10.1186/s12913-023-09886-7. PMID: 37612679; PMCID: PMC10463573.

monitoring, dose selection, or supporting efficacy. This draft guidance could help sponsors and researchers overcome the unique challenges with rare disease trials and should be revised to further address the unique challenges of rare disease drug development.

Recommendation 2: Clarify the applicability of the guidance to small populations and N-of-1 studies.

The draft guidance encourages use of alternative trial designs, which may be better suited for rare diseases by increasing the feasibility of conducting trials for diseases with limited patient numbers. NORD supports innovative approaches to rare disease research, which may ultimately bring safe and effective therapies to the market faster. Integrating RCTs into clinical care for rare disease patients presents different challenges than organizing large simple trials for widely prevalent, chronic diseases.

However, the draft guidance's limitation of scope to "drugs that are already FDA-approved" limits the guidance's applicability for rare diseases to repurposing studies. NORD consequently encourages the Agency to consider how the draft guidance could be revised to supplement its rare disease-specific guidances[6] to aid in innovative approaches to studying novel treatments for rare diseases. To augment the utility of this guidance, NORD strongly encourages the Agency to provide specific, nonproprietary exemplars of 'successful' utilization of point of care trials for rare diseases - including for N-of-1 and very small population trials. FDA should include best examples, practices, and use cases that highlight how drug sponsors and FDA may successfully apply this study design to rare disease drugs.

Recommendation 3: Provide additional guidance regarding COAs for rare disease trials integrated into clinical care.

Given the importance of uniform data collection and the selection of appropriate endpoints for clinical trials integrated into routine clinical care, NORD urges that FDA elaborate further on clinical outcome assessments (COAs) that may be acceptable as valid endpoints, and how sponsors should standardize COA collection during routine clinical care for rare disease patients.[7]

Common clinical laboratory measurements "for certain conditions" are cited as "appropriate outcomes to capture from clinical practice". (at 11) However, the heterogeneity of many rare diseases may render such biomarkers inconsistent, rendering rare disease patients as the experts on the manifestations of their disease, and clinical outcome assessments (COAs) as potential

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[6] FDA, Rare Diseases: Considerations for the Development of Drugs and Biological Products, December 2023, at https://www.fda.gov/media/119757/download; FDA, IND Submissions for Individualized Antisense Oligonucleotide Drug Products for Severely Debilitating or Life-Threatening Diseases: Clinical Recommendations, December 2021, at https://www.fda.gov/media/154663/download.

[7] Kim Y, Gilbert MR, Armstrong TS, Celiku O. Clinical outcome assessment trends in clinical trials-Contrasting oncology and non-oncology trials. Cancer Med. 2023 Aug;12(16):16945-16957. doi: 10.1002/cam4.6325. Epub 2023 Jul 8. PMID: 37421295; PMCID: PMC10501237.

endpoints.[8] Since many rare diseases do not have clear biomarkers or endpoints, COAs can help provide meaningful data for researchers to incorporate in their studies.[9] These COAs can include data like patient-reported outcomes (PROs) to assess symptoms and functional status (ex: patients with cystic fibrosis might report on how clear of mucus their lungs feel, patients with maple syrup urine disease might report on incidence of vomiting), in addition to numerical measures of biomarkers, although established and validated endpoints tend to be scarce for rare diseases. COAs are valuable clinical tools and must be leveraged in study designs discussed by this draft guidance, despite the difficulty of standardizing patient and doctor-reported outcomes across different health systems. Due to the value of these tools, COAs warrant further elaboration by FDA in the draft guidance.

Recommendation 4: Develop new partnerships through the Rare Disease Innovation Hub to apply the draft guidance and develop best practices through coordinated national rare disease clinical networks.

As previously mentioned, NORD encourages FDA to comment in the draft guidance on how rare disease clinical networks can organize point of care trials for small patient populations, but also urges the Agency to pursue public-private partnerships with national networks of care through the newly established Rare Disease Innovation Hub to demonstrate how the draft guidance can be best put into practice.

The NORD Rare Disease Centers of Excellence (RD CoE) network is the first national network of U.S. hospitals and medical institutions dedicated to diagnosing, treating and researching all rare diseases. The RD CoE network creates critical new connections for patients to resources and specialists across our nation – providing the optimal platform for demonstrating how clinical studies can be integrated into routine clinical care of rare disease patients. The Agency is urged to collaborate with the RD CoE network to learn about their data collection practices – as they best understand the capacity of health care providers to collect rare disease patient data – and adapt this guidance to reflect the practices already being undertaken. NORD believes the RD CoE network could be invaluable partners in refining and applying the draft guidance, given their critical insights and experience in integrating clinical studies and clinical care, which may serve to increase the inception of more rare disease RCTs.

We also encourage the Agency to consider applications of the draft guidance in fulfilling long-term post market commitments (ex: rare disease cell and gene therapies) and developing common data elements across both existing commitments and prospectively. The NORD IAMRARE® program presents another potential platform for data from point of care trials. The program was built by NORD with extensive input from FDA, NIH, patients, and as of December

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[8] FDA, Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments Into Endpoints For Regulatory Decision-Making, April 2023, at https://www.fda.gov/media/166830/download

[9] Source: https://toolkit.ncats.nih.gov/module/prepare-for-clinical-trials/working-with-industry-to-design-clinical-trials/clinical-outcome-assessments/#:~:text=Help%20Industry%20With%20Clinical%20Trial%20Design&text=Since%20many%20rare%20diseases%20do,tasks%20in%20the%20clinical%20setting.

17, 2024, holds 43 active registry/natural history studies, including more than 17,000 consented participants representing 140+ rare diseases, with 28 more IAMRARE® registries in active development. IAMRARE ® could integrate data from RCTs in clinical practice with existing natural history studies or other electronic health records, consolidating data in one platform and allowing for a wealth of information available for long-term post market commitment studies. This platform could be leveraged to support robust collection of RWE.

NORD again thanks FDA for the opportunity to provide comments on this important draft guidance, and we look forward to continuing the dialogue around integrating RCTs for drug and biological products into routine clinical practice, as well as other strategies to bring safe and effective rare disease drugs to market. For questions regarding NORD or the above comments, please contact Hayley Mason, Policy Analyst, at hmason@rarediseases.org.

Sincerely,

Hayley Mason, MPA
Policy Analyst
National Organization for Rare Disorders