August 24, 2026

Kyle Diamantis
Acting Commissioner
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Master Protocols for Drug and Biological Product Development; Draft Guidance [Docket No. FDA-2023-D-5259]

Dear Acting Commissioner Diamantas,

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the National Organization for Rare Disorders (NORD) appreciates the opportunity to comment on the Master Protocols Draft Guidance.

With a more than 40-year history, NORD is the pioneer patient advocacy group for the more than 30 million Americans living with a rare disease. An independent 501(c)(3) nonprofit, NORD is dedicated to individuals with rare diseases and the organizations that serve them. NORD, along with its more than 355 patient organization members, is committed to improving the health and well-being of people with rare diseases by driving advances in care, research, and policy. NORD believes that all individuals with a rare disease should have access to high quality, affordable health care that is best suited to meet their medical needs.

NORD strongly supports the Food and Drug Administration (FDA)'s role in ensuring that human medical products are safe and effective for their intended use. NORD went on record requesting the FDA ensure that its methods for evaluating products for rare diseases are fit for purpose.[1] Due to limited number of patients and rare disease treatments, trial designs that are not traditional two-arm, placebo-controlled trials may be more useful and more ethical for rare disease patients. To that end, NORD supports the use of novel trial designs, such as a master protocol for an umbrella trial, basket trial, or platform trial, when appropriate.

[1] See e.g., Citizen Petition from Haystack Project, Inc. et al., available at Docket FDA-2026-P-3666.

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The draft guidance places a great deal of importance on a traditional control group. However, placebo control groups are often not possible or ethical in rare diseases. In fact, lack of available therapies for comparison, as is common for rare diseases, is one of the key areas where external control designs have been most persuasive to FDA.[2] NORD urges the FDA to incorporate information from previously promulgated guidance on natural history, real-world evidence (RWE), and comparator arms into its guidance on master protocols. The draft guidance discusses exceptions to a placebo control arm; rather, NORD respectfully suggests that alternatives exist and should be considered more routinely.

Conclusion

NORD recommends the FDA provide additional guidance on the implementation of these novel trial designs that allow fit for purpose trials for rare diseases. We appreciate the opportunity to comment on this important issue and look forward to working with the Agency on behalf of the rare disease community.

Sincerely,

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[2] Mahta Jahanshahi et al., *The Use of External Controls in FDA Regulatory Decision Making*, Therapeutic Innovation & Regulatory Science 55(5):1019-1035 (May 20, 2021) doi: 10.1007/s43441-021-00302-y.

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