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U.S. Food and Drug Administration
10001 New Hampshire Ave
Silver Spring, MD 20903

May 2, 2023
Re: Docket No. FDA-2022-D-2983-0002 for "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry"

Dear Dr. Cavazzoni,

On behalf of the more than 25 million Americans living with one of the over 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(NORD) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to provide comments on the Agency's draft guidance "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products."

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 40 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; raised awareness and addressed key knowledge gaps; and advocated for policies that support the availability of and access to safe and effective therapies.

The vast majority of the more than 7,000 known rare diseases do not yet have an FDA-approved treatment, making continued progress in rare disease research and drug development critically important.[1] The unique challenges associated with rare disease research complicate both traditional randomized, double-blinded, placebo-controlled trials as well as alternative research approaches including observational studies, single-arm trials, and studies with external control arms. At the same time, nothing is more devastating to the rare disease community than dedicating considerable time and resources to a rare disease study only to find its flawed design and/or execution compromises the interpretability of the data to a point where it is inadequate to serve its regulatory purpose. In addition, the limited patient populations and financial realities of rare disease drug development generally make repeating a fatally flawed study impossible. Therefore, appropriately designing and conducting clinical studies the first time is often a matter of life and death for our patients.

Rare disease patients depend on robust evidence to trust in the safety and effectiveness of FDA-approved therapies and given the severity of unmet need, time is of the essence. NORD first and foremost appreciates FDA's efforts to provide guidance on the considerations for using externally controlled trials for drug development. While traditional randomized, double-blinded, placebo-controlled trials are the gold standard for clinical evidence of safety and effectiveness, they are not always feasible or ethical in

[1] FDA. (2022, March 4). *CDER continues to make rare diseases a priority with drug approvals*. U.S. Food and Drug Administration. Retrieved April 28, 2023, from https://www.fda.gov/news-events/fda-voices/cder-continues-make-rare-diseases-priority-drug-approvals-and-programming-speed-therapeutic

rare disease drug development.[2] In fact, both FDA and the International Conference for Harmonization (ICH) have previously released guidance on the use of external controls in drug development, emphasizing the role of external controls in situations where it is "unethical to run a placebo trial, the disease is well understood, and the trial has a measurable outcome." [3] Additional specific and actionable guidance on how to design the best possible externally controlled study when it is the only feasible option will be tremendously valuable to the rare disease community. As outlined in the guidance, the potential for uncontrolled residual bias and confounders are a significant concern with any externally controlled study. Unfortunately, the heterogeneity in disease manifestation, the small sample sizes, and the frequently scarce data on natural history and disease progression make controlling for these biases and confounders particularly challenging for rare diseases – and arguably limit the feasibility and applicability of the draft guidance in its current form to the rare disease field.

NORD also appreciates that the draft guidance is one of several guidance documents that have been developed on an interrelated range of topics such as Real-world data (RWD) and Real-world evidence (RWE), data standards, registries, Electronic Health Record (EHR) data, and common issues in rare disease drug development.[4] Finally, NORD appreciates FDA's engagement of patients through a variety of communication channels including the Reagan-Udall Foundation's Real-World Data Webinar series.[5] NORD values the opportunity to provide comments to ensure the draft guidance will provide meaningful and actionable advice to the rare disease community and would be delighted to support FDA in any efforts to further engage the rare disease community on this critically important issue.

Recommendation 1: Empower the rare disease community to design the best possible externally controlled trial given the unique challenges associated with rare disease drug development

External control arms and other types of RWD play an increasingly important role in rare disease drug development.[6] For instance, in a study analyzing approvals using historical data from 1999 to 2014, the FDA approved 60 new indications without the use of randomized controlled trials.[7] Similarly, another study found that 116 FDA approvals between 2019 and 2021 leveraged some form of real-world evidence.[8] Lack of available therapies for comparison, as is common for rare diseases, is one of the key

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[2] *Rare diseases: Common issues in drug development guidance for industry*. Food and Drug Administration. (2019, February). Retrieved April 28, 2023, from https://www.fda.gov/media/120091/download

[3] Jahanshahi, M., Gregg, K., Davis, G., Ndu, A., Miller, V., Vockley, J., Ollivier, C., Franolic, T., & Sakai, S. (2021, September). *The use of external controls in FDA Regulatory Decision making*. Therapeutic innovation & regulatory science. Retrieved April 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8332598/

[4] *Real-World Data Webinars*. Reagan-Udall Foundation. (2023). Retrieved April 28, 2023, from https://reaganudall.org/programs/research/real-world-data-webinars

[5] *Real-World Data Webinars*. Reagan-Udall Foundation. (2023). Retrieved April 28, 2023, from https://reaganudall.org/programs/research/real-world-data-webinars

[6] Thorlund, K., Dron, L., Park, J. J. H., & Mills, E. J. (2020, May 8). *Synthetic and external controls in clinical trials - A Primer for researchers*. Clinical epidemiology. Retrieved April 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7218288/

[7] Hatswell AJ, Baio G, Berlin JA, Irs A, Freemantle N. Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999-2014. BMJ Open. 2016 Jun 30;6(6):e011666. doi: 10.1136/bmjopen-2016-011666. PMID: 27363818; PMCID: PMC4932294.

[8] Purpura, C., Garry, E., Honig, N., Case, A., & Rassen, J. (2022). *The role of real-world evidence in FDA-approved new drug and Biologics License Applications*. Clinical pharmacology and therapeutics. Retrieved April 28,

areas where external control designs are most persuasive to FDA, further reinforcing the importance of this type of guidance for rare disease drug development.[9]

In fact, the vast majority of clinical trials with external control arms submitted to the FDA for purposes of drug approval involve rare diseases. A study of non-oncology FDA approvals from 2000 to 2019 identified 45 approvals where FDA accepted external control arm data to support pivotal trials, with 80% involving rare diseases.[10] Interestingly, half of the approvals for non-rare indications relied on previously conducted clinical studies or other published data as the external control while only three used retrospective natural history studies. In contrast, among the 36 rare disease approvals, retrospective natural history studies accounted for approximately half of the drug approvals, followed by 'baseline controls,' indicating that the types of external controls used to support rare disease drug approvals may be profoundly different from those used for non-rare diseases. In fact, a separate analysis identified 14 FDA approvals between 2018 and 2022 that incorporated RWE to support efficacy, all for orphan indications.[11] As a study of 49 oncology drugs approved by FDA and EMA from 1999 to 2014 without a randomized controlled trial demonstrates, this trend is also true internationally.[12,13]

Despite this very close link between rare diseases and external control arms, as it is written, the draft guidance is mostly applicable to non-rare diseases. Throughout the guidance, the topic of rare diseases is barely mentioned; in fact, a search of the document identified a single use of the term 'rare disease' – in a footnote on page 2. As a result, the unique challenges encountered when leveraging external controls in rare disease drug development are not considered nor addressed sufficiently in the guidance. For instance, the table on pages 12 and 13 of the draft guidance (see Table 1) provides a potentially useful reference summary of the considerations for assessing the comparability of the external control data but is lacking any specific guidance for how to apply the concepts or address these challenges in the rare disease space. Table 1 below outlines some of rare disease specific concerns that are currently missing from the guidance and that require additional guidance. Greater clarity about how the rare disease community can

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2023, from https://pubmed.ncbi.nlm.nih.gov/34726771/#:~:text=Finally%2C%20we%20qualified%20FDA's%20documented,evidence%20of%20safety%20or%20effectiveness.

[9] Jahanshahi, M., Gregg, K., Davis, G., Ndu, A., Miller, V., Vockley, J., Ollivier, C., Franolic, T., & Sakai, S. (2021, September). *The use of external controls in FDA Regulatory Decision making*. Therapeutic innovation & regulatory science. Retrieved April 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8332598/

[10] Jahanshahi, M., Gregg, K., Davis, G., Ndu, A., Miller, V., Vockley, J., Ollivier, C., Franolic, T., & Sakai, S. (2021, September). *The use of external controls in FDA Regulatory Decision making*. Therapeutic innovation & regulatory science. Retrieved April 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8332598/

[11] Silverman, B. (2022, September 12). *RWE's biggest role in US FDA approvals: External Controls for Breakthrough Rare Disease Therapies*. Pink Sheet. Retrieved April 28, 2023, from https://pink.pharmaintelligence.informa.com/PS146970/RWEs-Biggest-Role-In-US-FDA-Approvals-External-Controls-For-Breakthrough-Rare-Disease-Therapies

[12] Jahanshahi, M., Gregg, K., Davis, G., Ndu, A., Miller, V., Vockley, J., Ollivier, C., Franolic, T., & Sakai, S. (2021, September). *The use of external controls in FDA Regulatory Decision making*. Therapeutic innovation & regulatory science. Retrieved April 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8332598/

[13] Hatswell, A. J., Baio, G., Berlin, J. A., Irs, A., & Freemantle, N. (2016, June 30). *Regulatory approval of pharmaceuticals without a randomised controlled study: Analysis of EMA and FDA approvals 1999-2014*. BMJ open. Retrieved April 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4932294/

best navigate these challenges when applying the guidance framework in designing rare disease trials with external controls is urgently needed.

Table 1: Rare disease drug development challenges not currently addressed in FDA's draft guidance

Content from FDA Draft Guidance Text		NORD Comments
Focus of Comparison	**Considerations for Data Comparability**	**Rare Disease Specific Considerations that remain to be addressed in FDA's external control arm guidance:**
Time periods	Various aspects of clinical care may change over time, such as the standard of care for the condition of interest, types of treatments, supportive care regimens, and criteria for determining disease response or progression. Such temporal differences are difficult to address using statistical analyses alone. It is important to consider whether and how different time frames in the treatment arm and the external control arm impact the interpretability of study findings.	- Retrospective Natural History studies are the most commonly used type of external control arm in rare disease trials [14] - Patient registries, natural history studies, and clinical trials often capture a relatively large fraction of the overall rare disease patient population - A small number of providers are specialized in any given rare disease and tend to see a large fraction of the patient population
Geographic region	Standards of care and other factors (e.g., access to care) that affect health-related outcomes can vary across geographic regions and health care systems. A balance of participants or patients across geographic regions and health care systems in an externally controlled trial, when possible, can help reduce the impact of confounding based on such differences.	- Around 40% of rare disease patients travel more than 60 miles for specialized care and 17% have moved or considered moving to be closer to care. [15] - Small patient populations limit the number of rare disease patients in any specific geographic region - Concentration of rare disease specialists at large academic medical centers limits the number of health systems providing specialized care to rare disease patients

[14] Jahanshahi, M., Gregg, K., Davis, G., Ndu, A., Miller, V., Vockley, J., Ollivier, C., Franolic, T., & Sakai, S. (2021, September). *The use of external controls in FDA Regulatory Decision making*. Therapeutic innovation & regulatory science. Retrieved April 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8332598/

[15] NORD. (2019). *Barriers to rare disease diagnosis, care and treatment in the US: A 30 Year Comparative Analysis*. National Organization for Rare Disorders . Retrieved May 1, 2023, from https://rarediseases.org/wp-content/uploads/2022/10/NRD-2088-Barriers-Survey-Report_Infographic_FNL.pdf

Diagnosis	The criteria used to establish a diagnosis may differ based on practice variation or may have changed in the interval between when the treatment arm of the trial was conducted and when the data for the external control arm were collected. Sponsors should consider the diagnostic standards used and whether relevant clinical tests to establish a diagnosis were conducted and reported equally across the compared arms	- Many rare disease patients endure a diagnostic odyssey of 5 -7 years before the correct diagnosis - Most rare diseases are genetic; initial diagnosis may lead to screening and diagnosing cases in additional family members - New diagnostic tests, including whole-genome sequencing and exome sequencing, as well as additions to the newborn screening panel impact diagnosis - New rare diseases continue to be diagnosed and rare disease subtypes defined
Prognosis	Based on demographic and clinical characteristics—and if sufficient knowledge of relevant prognostic factors is available—prognostic indicators for the participants or patients in each arm of the trial should be evaluated and shown to be of sufficient similarity to permit an unbiased assessment of the treatment-outcome association.	- The natural history and disease progression of most rare disease is incompletely understood, and often highly heterogenous[16] - The small sample sizes complicate statistically rigorous comparisons
Treatments	Attributes of the treatment of interest—including drug formulation, dose, route of administration, timing, frequency, and duration as well as specific rules for dose modifications, interruptions, discontinuations, and adherence—will have been prespecified or measured in the treatment arm. In contrast, specific aspects of a comparator treatment (as applicable) in the external control arm may not have been protocol-driven depending on the data source. Accordingly, sponsors should assess whether the external control arm data can be meaningfully compared to the treatment arm data	- Most rare diseases lack disease-specific ICD-10 codes, complicating the use of RWD - The small sample sizes complicate statistically rigorous comparisons
Other treatment-	Various treatment-related considerations, when relevant, include (1) previous treatments received (e.g., lines of therapy	- Many rare disease patients are medically complex and rare diseases

[16] *Rare diseases: Common issues in drug development guidance for industry*. Food and Drug Administration. (2019, February). Retrieved April 28, 2023, from https://www.fda.gov/media/120091/download

related factors	in patients with cancer), (2) medications received concomitantly that can affect the outcome of interest, or (3) predictive biomarkers (e.g., genomic testing) related to the treatment of interest. When differentially distributed across groups being compared, such factors can threaten an assessment of the drug-outcome association.	often affect multiple organ systems concomitantly - Off-label use is common among rare disease patients - Rare disease communities tend to be tight-knit and new therapy adoption tends to be rapid - Predictive (and qualified) biomarkers are scarce for many rare disease
Follow-up periods	Designation of the index date should be consistent between the treatment arm and the external control arm, and the duration of follow-up periods should be comparable across compared arms	- Rare disease communities tend to be tight-knit and many rare disease registries are operated by and for patients, making longitudinal follow-up more feasible
Intercurrent events	The relevance of intercurrent events across treatment arms should be assessed, including differential use of additional therapies after initiation of the treatment of interest.	- Rare disease patients tend to see multiple providers including several specialists to manage their condition and often use a number of different therapies at the same time
Outcome	Whether endpoints used in an externally controlled trial can be reliably and consistently measured across the external control arm and the treatment arm will be influenced by several factors, including the definitions of the endpoints, the data source for the external control arm, and the potential for the outcome to be influenced by knowledge of treatment received. In addition, sponsors should be able to apply the same criteria for the evaluation and timing of outcome assessments across both arms of the externally controlled trial	- Clinical outcome assessments are quite commonly used in rare disease drug development - Established and validated endpoints tend to be scarce for rare diseases[17]
Missing data	The extent of missing data in the external control arm should be assessed before conducting an externally controlled trial to evaluate feasibility (when such data are available). When analyzing results from such a trial, the extent of missing data in both the treatment and external control arms should be assessed to examine the potential impact of missing data.	- Small sample sizes potentially increase the impact of missing data and complicate sensitivity analyses and assessments of non-random missingness - Rare disease patients often seek care from multiple providers, increasing interoperability and data completeness challenges

[17] *Rare diseases: Common issues in drug development guidance for industry*. Food and Drug Administration. (2019, February). Retrieved April 28, 2023, from https://www.fda.gov/media/120091/download

Based on these concerns, NORD offers the following specific recommendations:

1.a. Given the substantial number of externally controlled trials that are conducted for rare diseases, tailor this draft guidance to be compatible with the unique challenges of rare disease drug development. NORD recognizes that some of these rare disease specific issues are partially addressed in other FDA guidance documents."[18,19] Where more specific and relevant guidance for rare diseases is available from other sources, it would be beneficial to provide a concrete reference and briefly summarize the pertinent information relevant to rare diseases in this guidance. Moreover, where multiple guidance documents may seemingly contradict each other, clarify the relationship among the guidance documents and how the Agency's thinking on the issue may have evolved over time. Finally, where concrete and practical guidance on applying the guidance in a way that addresses the unique challenges associated with rare diseases is lacking, we urge FDA to add this specificity to the guidance.

1.b. Provide an appendix or supplementary materials with additional details and illustrative examples to further clarify the Agency's thinking and to provide actionable advice for drug sponsors on how to successfully apply the concepts in rare disease drug development. FDA should include examples and use cases that highlight how drug sponsors and FDA have successfully navigated these challenges in the past and how specifically the Agency may weigh the factors outlined in the guidance given the unique challenges in rare disease drug development. Where the Agency has incorporated further details and examples like this in other relevant guidance documents, it has usually proven exceedingly helpful for our community; see for instance PFDD Guidance 1: Collecting Comprehensive and Representative Input;[20] PFDD Guidance 3: Selecting, Developing or Modifying Fit-for-purpose Clinical Outcome Assessments;[21] Submitting Documents using real-world Data and Real-world evidence to FDA for Drug and Biological Product;[22] Recommendations for the Submission of LOINC Codes in Regulatory Applications to the US Food and Drug Administration.[23] Discussion of illustrative examples referencing specific drugs and their completed FDA reviews should not be impeded by confidentiality considerations, since discussion of such examples can rely upon the summary basis for approval, advisory committee proceedings, and other publicly available information.

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[18] Center for Drug Evaluation and Research. (2019, March). Rare diseases: Natural history studies for drug development. U.S. Food and Drug Administration. Retrieved May 2, 2023, from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/rare-diseases-natural-history-studies-drug-development

[19] *Rare diseases: Common issues in drug development guidance for industry*. Food and Drug Administration. (2019, February). Retrieved April 28, 2023, from https://www.fda.gov/media/120091/download

[20] Center for Drug Evaluation and Research. (2023). Patient-focused drug development guidance series. U.S. Food and Drug Administration. Retrieved April 28, 2023, from https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

[21] Center for Drug Evaluation and Research. (2023). Patient-focused drug development guidance series. U.S. Food and Drug Administration. Retrieved April 28, 2023, from https://www.fda.gov/drugs/development-approval-process-drugs/fda-patient-focused-drug-development-guidance-series-enhancing-incorporation-patients-voice-medical

[22] Center for Drug Evaluation and Research (CDER). (2022, September). Submitting documents using real-world data and real-world evidence to ... U.S. Food and Drug Administration. Retrieved April 28, 2023, from https://www.fda.gov/media/124795/download

[23] *Recommendations for the submission of LOINC codes in regulatory ...* U.S. Food and Drug Administration. (2017, November). Retrieved April 28, 2023, from https://www.fda.gov/media/109376/download

Recommendation 2: Not all external data sources and use cases are created equal, and external controls can support clinical trials in multiple ways; a framework and more nuanced guidance is needed to adequately guide sponsors through the external control trial design process

Ultimately, studies including external control arms must be fit for purpose, just like other regulatory studies. As mentioned in the draft guidance, "the suitability of an externally controlled trial design warrants a case-by-case assessment […]."[24] NORD strongly agrees with this sentiment. For instance, not all studies leveraging external control arms may be intended as pivotal studies. Moreover, external data may be used to augment, rather than replace, internal control arms, and each external control data type has its unique set of strengths, limitations, and inherent biases that in combination may provide a richer and more accurate and complete assessment of a drug's safety and effectiveness. Rather than establishing a seemingly arbitrary dichotomy between randomized placebo-controlled trials and externally controlled trials, FDA should create a framework that allows sponsors to adequately consider these nuances as they apply to their specific use case.

In fact, various studies in recent years have assessed how external or hybrid control designs, which supplement an underpowered control group with real-world data, compare to traditional randomized controlled trials across a variety of use cases spanning numerous populations, organ systems, and rare as well as non-rare indications. For instance, *Chen et al.* (2019) developed a propensity-score based method to augment clinical trial data with RWD while down-weighing the specific information contributed by the RWD based on the propensity of each patient to be included in the RCT rather than the RWD, and demonstrated the value of this approach through simulation studies.[25] Similarly, *Magaret et al.* assessed the feasibility of leveraging external historical controls to augment or replace traditional concurrent placebo controls in trials evaluating the efficacy of azithromycin in reducing exacerbation risk among cystic fibrosis patients.[26] After adjusting for baseline differences between the populations, hazard ratios in the augmented and externally controlled trials appeared qualitatively comparable to those in the original placebo-controlled trial, albeit both the comparability of the controls and the statistical methodology impacted the residual bias in the estimation of the treatment effect.[27] *Chen* et al. (2021) used RWD from a large clinical research network to simulate a Phase III double-blinded Alzheimer's disease trial with parallel control groups that compared two donepezil formulations.[28] Specifically, the authors compared

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[24] *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry*. Food and Drug Administration. (2023, February). Retrieved April 28, 2023, from https://www.fda.gov/media/164960/download

[25] Chen, W.-C., Wang, C., Li, H., Lu, N., Tiwari, R., Xu, Y., & Yue, L. (2019, September 4). *Propensity score-integrated composite likelihood approach for augmenting the control arm of a randomized controlled trial by incorporating real-world data*. Taylor & Francis. Retrieved April 28, 2023, from https://www.tandfonline.com/doi/abs/10.1080/10543406.2020.1730877

[26] Magaret, A., Warden, M., Simon, N., Heltshe, S., Retsch-Bogart, G., Ramsey, B., & Mayer-Hamblett, N. (2022, March). *A new path for CF clinical trials through the use of historical controls*. NIH National Library of Medicine. Retrieved March 9, 2023, from https://pubmed.ncbi.nlm.nih.gov/34879997/

[27] Magaret, A., Warden, M., Simon, N., Heltshe, S., Retsch-Bogart, G., Ramsey, B., & Mayer-Hamblett, N. (2022, March). *A new path for CF clinical trials through the use of historical controls*. NIH National Library of Medicine. Retrieved March 9, 2023, from https://pubmed.ncbi.nlm.nih.gov/34879997/

[28] Chen, Z., Zhang, H., Guo, Y., George, T. J., Prosperi, M., Hogan, W. R., He, Z., Shenkman, E. A., Wang, F., & Bian, J. (2021, May 14). *Exploring the feasibility of using real-world data from a large clinical data*

the performance of a simulated trial with an external control arm based on standard-of-care and a two-arm simulation to the actual clinical trial data (i.e., NCT00478205), and found similar serious adverse events rates albeit the rates in the simulations were somewhat higher than in the original trial.[29] Focusing on glioblastoma data, *Ventz et al.* (2019) compared the statistical performance of externally controlled trials to that of randomized and single-arm trials, and found that external control data reduced bias by up to 30 percent compared to single-arm trials while improving the study's power compared to a traditional randomized trial design.[30] *Schroeder et al*. successfully replicated a phase III randomized controlled trial for metastatic colorectal cancer using electronic health record (EHR) data.[31] *Ventz et al*. (2022) further proved the value of hybrid controlled trials using simulations and data from small cell lung cancer and glioblastoma patients, and found hybrid trial designs potentially advantageous compared to externally controlled as well as randomized trials. [32] Similarly, *Shan et al*. recently published a simulation study comparing different single and hybrid control methods and found several of the evaluated statistical methods effective at reducing potential biases, at least under the evaluated conditions, albeit at a cost of statistical efficiency.[33] As these results show, blended approaches hold a tremendous promise, and a dichotomous view of internal vs. external controls unnecessarily restricts the usefulness of external data sources in clinical trials. Further guidance is needed, however, on how these more novel approaches fit into FDA's thinking about external control arms, and how these approaches can be appropriately leveraged specifically in rare disease drug development.

At the same time, not all externally controlled trials are created equal. As several recent reviews on the topic point out, a variety of data types and approaches have been used in regulatory decision-making in

research network to simulate clinical trials of alzheimer's disease. Nature News. Retrieved April 28, 2023, from https://www.nature.com/articles/s41746-021-00452-1

[29] Chen, Z., Zhang, H., Guo, Y., George, T. J., Prosperi, M., Hogan, W. R., He, Z., Shenkman, E. A., Wang, F., & Bian, J. (2021, May 14). *Exploring the feasibility of using real-world data from a large clinical data research network to simulate clinical trials of alzheimer's disease*. Nature News. Retrieved April 28, 2023, from https://www.nature.com/articles/s41746-021-00452-1

[30] Ventz, S., Lai, A., Cloughesy, T. F., Wen, P. Y., Trippa, L., & Alexander, B. M. (2019, August 15). *Design and evaluation of an external control arm using prior clinical trials and real-world data*. American Association for Cancer Research. Retrieved April 28, 2023, from https://aacrjournals.org/clincancerres/article/25/16/4993/125037/Design-and-Evaluation-of-an-External-Control-Arm

[31] Schroeder, C., Lawrence, M., Li, C., Lenain, C., Mhatre, S., Reyes-Rivera, I., & Bretscher, M. (2021, April 23). *Building External Control Arms From Patient-Level Electronic Health Record Data to Replicate the Randomized IMblaze370 Control Arm in Metastatic Colorectal Cancer*. JCO Clinical Cancer Informatics. Retrieved April 28, 2023, from https://ascopubs.org/doi/10.1200/CCI.20.00149

[32] Ventz, S., Khozin, S., Louv, B., Sands, J., Wen, P., Rahman, R., Comment, L., Alexander, B., & Trippa, L. (2022, October 2). *Design and evaluation of an external control arm using prior clinical trials and real-world data*. Clinical cancer research : an official journal of the American Association for Cancer Research. Retrieved April 28, 2023, from https://pubmed.ncbi.nlm.nih.gov/31175098/

[33] Shan, M., Faries, D., Dang, A., Zhang, X., Cui, Z., & Sheffield, K. M. (2022, February 16). *A simulation-based evaluation of statistical methods for hybrid real-world control arms in clinical trials - statistics in biosciences*. SpringerLink. Retrieved April 28, 2023, from https://link.springer.com/article/10.1007/s12561-022-09334-w

the US and other countries, each use case with its unique strengths and limitations. [34,35,36] Numerous factors including the type of external control, selected time frame and prospective or retrospective nature of data collection, type of comparator arm, type of endpoint, selected outcome measure, expected effect size, patient population, frequency of intercurrent events and censoring, and many other factors, are tightly interconnected and together determine the quality of the study design. Similarly, not all statistical approaches to external control arms are created equal. *Loiseau et al*., for instance, compared several common propensity score based and outcome modelling based techniques for trial replication, swapping trial arms from five different clinical trials, and found that outcome prediction-based approaches reduced estimation error and increased statistical power compared to propensity score-based approaches.[37]

Based on these concerns, NORD offers the following specific recommendations:

2.a. Add granularity, depth, and nuance to the guidance by recognizing the complementary nature of external and internal control data and provide more specific guidance on how to successfully leverage external controls including a summary of the strengths and limitations of different data types and analysis approaches. NORD appreciates that the benefits and drawbacks of the different data sources and techniques are highly context-specific, that designing externally controlled trials involves a unique set of trade-offs that must be weighted carefully, and we understand why "FDA does not recommend a particular approach to analyzing data from externally controlled trials. No single statistical or analytical method will be suitable for all trials involving external control arms, and potential approaches should be discussed with the appropriate FDA review division."[38] However, the current guidance does not provide nearly sufficient detail to begin a meaningful discussion of the trade-offs involved; even if there is not a single best approach to designing external control arm trials, FDA should develop further guidance to help identify the strengths and weaknesses of each approach, to describe how different data types and approaches can complement each other, and to meaningfully guide sponsors in the selection of the most appropriate approach or approaches for a given drug development program.

2.b. As the review of the recent literature shows, the field of RWD and RWE for regulatory decision-making is rapidly maturing and the understanding of the specific tradeoffs in each use

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[34] Mishra-Kalyani, P. S., Amiri Kordestani, L., Rivera, D. R., Singh, H., Ibrahim, A., DeClaro, R. A., Shen, Y., Tang, S., Sridhara, R., Kluetz, P. G., Concato, J., Pazdur, R., & Beaver, J. A. (2022, January 9). *External Control Arms in oncology: Current use and future directions*. Annals of Oncology. Retrieved April 28, 2023, from https://www.annalsofoncology.org/article/S0923-7534(22)00006-0/fulltext

[35] Yap, T., Jacobs, I., Baumfeld Andre, E., Lee, L., Beaupre, D., & Azoulay, L. (2021, December 10). *Application of real-world data to external control groups in Oncology Clinical Trial Drug Development*. Frontiers. Retrieved April 28, 2023, from https://www.frontiersin.org/articles/10.3389/fonc.2021.695936/full

[36] Kim, T.-E., Park, S.-I., & Shin, K.-H. (2022, September). *Incorporation of real-world data to a clinical trial: Use of external controls*. Translational and clinical pharmacology. Retrieved April 28, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9532857/

[37] Loiseau, N., Trichelair, P., He, M., Andreux, M., Zaslavskiy, M., Wainrib, G., & Blum, M. G. B. (2022, December 28). *External Control Arm Analysis: An evaluation of propensity score approaches, G-computation, and doubly debiased machine learning - BMC Medical Research methodology*. BioMed Central. Retrieved April 28, 2023, from https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-022-01799-z

[38] *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry*. Food and Drug Administration. (2023, February). Retrieved April 28, 2023, from https://www.fda.gov/media/164960/download

case is evolving; to complement the guidance documents, FDA should regularly review the literature and develop and refine best practices, including those specific to use cases among rare diseases. Publishing this information in peer-reviewed literature rather than in guidance will allow FDA to provide more timely and nuanced updates while meaningfully shaping the academic field.

Recommendation 3: Meaningfully engage the rare disease patient, provider, and academic community in the discussion of appropriate external control arm use

As outlined above, external control arms play a vital role in rare disease drug development. At the same time, conducting clinical trials with external control arms is often particularly challenging for rare diseases given the limited natural history data, small populations, and complex disease pathology.[39] In the draft guidance, the Agency therefore recommends that, "sponsors should consult with the relevant FDA review division early in a drug development program about whether it is reasonable to conduct an externally controlled trial instead of a randomized controlled trial."[40]
In the rare disease space, patient advocacy groups, academic researchers, and small biotech companies in the pre-revenue phase play an outsized role in research and data collection including patient-led disease registries and other RWD sources that often serve as external controls or at least meaningfully inform clinical trial design. It is vitally important that these stakeholders understand FDA's current thinking on external control arms, have realistic expectations about the acceptability of RWD sources to support approvals, and that they are equipped with the information and tools needed to collect regulatory-grade data. These groups need additional outreach to effectively understand and leverage FDA's guidance documents.

Many of these stakeholders do not have ample experience interacting with FDA review divisions; they often lack awareness of the need to engage early, lack the understanding of FDA organizational structures to identify the appropriate contacts, and often do not have the tools and knowledge to engage effectively. In fact, in NORD's recent membership survey, 21% of queried patient advocacy groups identified guidance for how to request a meeting with FDA as a key gap, and 23% wanted guidance on how to prepare for a meeting with FDA. As a result, critical rare disease stakeholder groups are unlikely to proactively and effectively consult with the relevant FDA division early and often in the drug development process, increasing the risk of externally controlled studies and data that ultimately fail to meet FDA's regulatory standards.

Based on these concerns, NORD offers the following specific recommendations:

3. NORD strongly encourages the Agency to engage rare disease patients, providers, and academic researchers more proactively on this topic by hosting webinars, workshops, and partnering with trusted advocacy organizations to cover topics to give better guidance on the use of these external controls. FDA's LEADER 3-D program provides one meaningful and timely avenue to create awareness

[39] FDA. (2022, December 31). Rare diseases at FDA. U.S. Food and Drug Administration. Retrieved March 9, 2023, from https://www.fda.gov/patients/rare-diseasesfda#:~:text=Drug%2C%20biologic%2C%20and%20device%20development,make%20conducting%20clinical%20trials%20difficult.

[40] *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry*. Food and Drug Administration. (2023, February). Retrieved April 28, 2023, from https://www.fda.gov/media/164960/download

and disseminate the relevant information to this stakeholder group. However, combining a variety of approaches, based on successful existing programs, will likely be most successful. For instance, on April 13, 2023, representatives from the FDA and the Reagan-Udall Foundation partnered to discuss in a webinar the draft guidance and were met with various questions on how to use external controls and best mitigate confounding evidence and bias. [41] This webinar provided a forum to answer questions from advocates, pharma representatives, and individuals who had questions regarding the use of external controls by having FDA representatives accessible and available. Similarly, on May 2 and 3, 2023 FDA and Johns Hopkins University partnered on a public workshop on Addressing Challenges in the Design and Analysis of RARE Disease Clinical Trials: Considerations and Tools.[42]

In hosting webinars specific to engaging rare disease stakeholders on the use of external control arms and other types of RWD and RWE, some topics to consider include:

1. The benefits, mechanisms, and best practices of early engagement with FDA in rare disease drug development
2. How to assess for bias and confounding evidence when using external control arms for rare disease drug development
3. Best practices for using external control arms and how to assess when to use external controls specifically in rare disease drug development
4. Considerations for the various types of external controls and their strengths and weaknesses specifically for rare disease dug development
5. Considerations and best practices for the collection and use of Natural History Studies and other RWE/RWD in rare disease drug development

NORD again thanks FDA for the opportunity to provide comments on this important draft guidance, and we look forward to continuing the dialogue around external control arms, RWE/RWD, 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 Karin Hoelzer. Director of Policy and Regulatory Affairs, at khoelzer@rarediseases.org or Hayley Mason. Policy Analyst, at hmason@rarediseases.org

Sincerely,

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[41] *Real-world evidence Webinar series: Considerations for the design and conduct of externally controlled trials for drug and Biological Products Draft Guidance for Industry*. Reagan-Udall Foundation. (2023). Retrieved April 28, 2023, from https://reaganudall.org/news-and-events/events/real-world-evidence-webinar-series-considerations-design-and-conduct

[42] Center for Drug Evaluation and Research (CDER), & Johns Hopkins University's Center of Excellence in Regulatory Science and Innovation. (2023, May). *FDA CDER & JHU CERSI Workshop*. U.S. Food and Drug Administration. Retrieved May 2, 2023, from https://www.fda.gov/drugs/news-events-human-drugs/fda-cder-jhu-cersi-workshop-addressing-challenges-design-and-analysis-rare-disease-clinical-trials