May 2, 2023

Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: FDA-2022-D-2983 Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

To Whom It May Concern:

The Robert J. Margolis, MD Center for Health Policy at Duke University ("Duke-Margolis" or "the Center") appreciates the opportunity to comment on the Food and Drug Administration's "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products; Guidance for Industry" ("the draft guidance") document. We are encouraged by the FDA's commitment to advancing real-world data (RWD) and real-world evidence (RWE).

Established in January 2016, Duke-Margolis is both an academic research center and a policy laboratory where stakeholders can come together to analyze, propose, and evaluate ways to improve health in the United States and beyond. The Center's mission is to improve health and health care value through practical, innovative, and evidence-based policy solutions. By catalyzing Duke University's leading capabilities, we conduct research and convene activities focused on biomedical innovation and regulatory policy. Thought leadership on the regulatory acceptability of RWD and RWE is a dedicated goal for our team.

Duke-Margolis has two complementary programs dedicated to advancing RWD and RWE science and policy for regulatory use. First, under a cooperative agreement with the FDA's Center for Drug Evaluation and Research (CDER), Duke-Margolis has held several expert workshops and public conferences related to RWE and RWD regulatory acceptability. Second, the Center has formed a multi-stakeholder collaboration ("RWE Collaborative") with the intent and goal of strengthening the development and potential applications of RWD and RWE. RWE Collaborative member organizations and their expert representatives are listed in Appendix I. The RWE Collaborative is guided by an advisory group comprised of leaders from health care industries, academia, and others who are developing practical approaches to support the generation and use of regulatory-grade RWE. To date, Duke-Margolis' RWD and RWE activities have spanned several public and private meetings, the convening of multiple working groups, and the publication of eight major white papers available on our website.

Through this work, Duke-Margolis aims to support collaborative strategies to advance the effective development and use of RWD and RWE. The comments and considerations below represent the thinking and recommendations of expert Center faculty and staff, which have been informed by RWE Collaborative activities and expertise. Duke-Margolis looks forward to continuing our work with the FDA, the RWE Collaborative, and other stakeholders to move RWE policy forward.

Duke-Margolis, as part of Duke University, honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important and pertinent issues. The Center's comments herein are informed by RWE Collaborative members but may not represent the opinions of every RWE Collaborative member. This comment letter is not intended to limit the ability of RWE Collaborative members to provide their own comments on behalf of their independent organizations.

Our comments for the draft guidance focus on the following areas:

- **FDA Access to External Control Arm Data**
- **RWD Submissions and Feasibility Checks**
- **Considerations for the CDISC format**
- **Alignment of real-world and trial data assessments**

Within these areas we suggest the following next steps for the FDA and broader stakeholder communities:

- Convene a multistakeholder workshop to develop and refine ideas for the development of a cloud-based or data enclave platform to facilitate FDA access to patient-level RWD without compromising propriety or privacy.
- Continue advancing work and discussions on data submission standards for RWD sources along the spectrum of randomized, interventional studies to non-randomized, noninterventional studies.
- Leverage the Advancing RWE Program to provide more direct, publicly available feedback on how RWD/RWE have been considered in regulatory review processes, including for RWD-based external control arms.
- Provide guidance around external control arm methods and uses that might reach beyond the present draft guidance (e.g., summary-level estimates, hybrid controls).

FDA Access to External Control Arm Data

While it is reasonable for the FDA to request access to RWD akin to randomized controlled trials (RCTs) data, FDA must function within certain operational confines to access raw patient-level RWD, including external control arm data, submitted for regulatory review. These sources are subject to certain data governance and legal restrictions regarding data propriety and privacy. Thus, exploring new and existing pathways to facilitate patient-level data exchanges between FDA and study sponsors warrants further discussion and examples with respect to the present draft guidance.

Trial sponsors rarely own or have reason to own RWD that is leveraged for an interventional study, which raises concerns about data propriety. We appreciate the FDA's recognition in the guidance that private parties will have to coordinate data access; although, the level of access the FDA is requesting could add trial burden that might render external controls infeasible. Stakeholders frequently contract to use secondary health data which itself was collected by another party. Existing contracts will routinely disallow the further transfer of patient data, and that paradigm exists to protect patients and encourage their participation in studies. Altering this paradigm or attempting to trace each patient for revised or

updated consent is not always feasible. Since it may not be possible to provide complete access in all cases, we recommend that the FDA build on their prior Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products guidance to identify and disseminate examples of regulatory submission pathways that provide the least amount of friction and minimize data privacy/propriety risk with respect to sharing patient-level data with the FDA.

While the Federal Food, Drug, and Cosmetic Act codifies some expectations for the FDA's access to data, the data collected for external control arm execution is regulated and protected by The Health Insurance Portability and Accountability Act of 1996 (HIPAA). Even if this data were investigators and sponsors to share (i.e., they had the necessary ownership of the data), that propriety would not necessarily beget the right to share patient data in a way that potentially risks compromising patient privacy. We ask that the FDA address potential incompatibilities in the differing statutory requirements across HHS, FDA, and state rules, and how the agency sees them intersecting. It is essential that data privacy is not compromised by unclear chains of data custody. For instance, what are possible differences in certain types of data having greater or lesser privacy protections in accordance with the law? Does it make sense for the FDA to be responsible for data custodianship and protection as owners of protected health information? The questions are especially salient for rare disease patients who are most likely to become re-identified among a de-identified cohort. Diseases with small patient populations—like those ideal for leveraging external control arms—are at risk for individual reidentification simply due highly specific study inclusion criteria or parameters. Further concerns arise if re-identifiable data are not explicitly exempt from Freedom of Information Act (FOIA) requests.

Our proprietary and privacy concerns raise another consideration around how best to provide FDA with patient-level RWD to inform regulatory review. While there are examples of clinical studies leveraging RWD and passing inspections, questions remain for studies utilizing larger, aggregated data sources.[1] A solution may be for sponsors and data aggregators to provide the FDA with access to the data without transferring possession. The agency could be provided with necessary access and visibility to query, audit, and replicate analyses without the external control data leaving the owner's system. Striking a balance in this way between FDA needs and sponsor and data provider perspectives could ameliorate aforementioned concerns on privacy and proprietary data. This might necessitate cloud-based platforms or data enclaves that the FDA can use to access the data as well as documentation providing audit trails and related information as discussed in this guidance and elsewhere.[2] Advancements led by other federated and distributed models, such as Sentinel, may be instructive here. A secure, online portal could be built allowing stakeholders to link their data to a common platform accessible to FDA. While expense of development is a limiting factor, there are a variety of approaches that the FDA might find feasible. Furthermore, secure access to full, living platforms of audited data could provide more insights for FDA decision-making as opposed to possessing reams of data submitted with limited context. A multistakeholder workshop would be a good venue to develop and refine ideas for the development of such a platform.

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[1] "FDA Approves Alpelisib for PIK3CA-Related Overgrowth Spectrum."

[2] "Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations, Questions and Answers: Guidance for Industry."

The RWE Collaborative—a group of diverse, solution-oriented stakeholders and subject matter experts—is prepared to embrace the FDA's call for data aggregators and product sponsors to align on data access agreements. It would be a great help for the FDA to provide greater detail on what the agency imagines would be the scope of such agreements. It would be beneficial for stakeholders to have a clearer understanding of which questions should be asked and debates held when drafting language for these new types of agreements. While we certainly do not expect the FDA to provide contract language, clear examples of what the FDA expects access to, that can be readily incorporated into contract language, would be immensely helpful for stakeholders seeking to develop data agreements with an eye towards regulatory submissions.

RWD Submissions and Feasibility Checks

The FDA correctly emphasizes the importance of feasibility checks; however, the parameters suggested by the draft guidance may be impractical when applied. Investigators may find it challenging to finalize their analysis protocols for FDA review as early in the study development as the FDA deems ideal. As the earliest phases of the study design unfold, revisions for logistics and real-time changes in medical/regulatory conditions are often needed. Requiring study protocols to be set in stone too early would necessitate either:

A) Potentially getting insight into exposure vs. outcome information prematurely by evaluating which protocols fit the study prior to analysis (i.e., "peeking"), or
B) Finalizing a faulty study protocol that would otherwise be refined in accordance with normal, scientifically sound procedures.

The former is unacceptable prior to pre-specification, and the latter could render the study ineffective and unproductive by locking into a protocol that is quickly revealed to be flawed. Flexibility is needed regarding the timing of statistical analysis plan (SAP) submission and the ability to make SAP and protocol amendments. A staggered protocol approach leveraging time stamps to build an audit trail of scientifically sound decision making could be helpful here. It would be informative to have guidance on separating protocol development from data source selection in the submission process. Please see our comments on the "Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products" draft guidance, where we discuss in more depth a potential staggered protocol approach to address these challenges.[3] We additionally appreciate the FDA's March 2023 draft guidance on "Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations Questions and Answers" which provides recommendations for audit trail implementation.[4] That information should be helpful to external control submitters seeking to determine feasibility while not favoring specific results.

[3] Mark McClellan et al., "RE: FDA-2021-D-1214 Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products," March 8, 2022.
[4] "Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations, Questions and Answers: Guidance for Industry."

Considerations for the CDISC format

The CDISC format is not ideal for submitting studies that use real-world data as noted in prior comments from Duke-Margolis and others on the "Data Standards for Drug and Biological Product Submissions Containing Real-World Data" guidance.[5] We thank the FDA for acknowledging needed additional work and providing initial direction on CDISC formatting in that data standards guidance document.[6] We ask the FDA to continue working towards greater clarity on expectations for the formatting of RWD sources in submissions to the FDA that consider uses of RWD along the spectrum of randomized, interventional studies to non-randomized, noninterventional studies. While medical product submissions to the FDA currently require analytic files to be transformed into CDISC data standards, which are intended to format traditional clinical trial data, there is a risk that some data richness could be lost during these transformations and formatting when submitted datasets are derived from RWD. A more flexible approach might involve leveraging a more RWD appropriate data model. Submissions that that combine RWD and traditional trial data—as in external controls—additionally present a unique formatting challenge. As the FDA drafts the "further guidance and/or [updates to] the Catalog with standards for study data that are derived from RWD sources," mentioned in the current draft data standards guidance, we ask that formatting considerations for studies combining RWD and traditional data be explored.[7] In the interim, we encourage continued collaboration of stakeholders and CDISC on relevant mapping activities to minimize these challenges.

Alignment of real-world and trial data outcome assessments

The draft guidance rightly points out the challenges of outcomes when leveraging external controls due to differences in assessment timing and frequency, differences in trial versus routine care measurement approaches and rigor (e.g., use of RECIST criteria in trials or different diagnostic testing approaches by setting), and ability to blind treatment. This discussion in the guidance and other discussion on the limitations of retrospective data suggest that prospective external control arm data is collected on a schedule matching the treatment arm is the preferred approach for trials with external controls. We do not disagree with this and suggest that the FDA makes clear in the guidance the benefits of intentional prospective RWD capture. However, we feel it is important to point out that flexibility is warranted in some circumstances. For example, such prospective external control data collection is likely not appropriate for rare disease studies where it might be challenging to ask patients to be on a trial arm with no treatment option. In this circumstance, stakeholders in the field should explore robust methodologies for analyzing outcomes compared to external control data that do not match exactly with the frequency or measurement choices made in the trial arm. A framework for determining this data's fitness for use in an external control arm would be beneficial, and the SPIFD2 Framework could provide some direction.[8]

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[5] Mark McClellan et al., "RE: FDA-2021-D-0548 Data Standards for Drug and Biological Product Submissions Containing Real-World Data," February 4, 2022.
[6] "Data Standards for Drug and Biological Product Submissions Containing Real-World Data Guidance for Industry."
[7] "Data Standards for Drug and Biological Product Submissions Containing Real-World Data Guidance for Industry."
[8] Gatto et al., "A Structured Process to Identify Fit-for-Purpose Study Design and Data to Generate Valid and Transparent Real-World Evidence for Regulatory Uses."

The FDA has in the past approved new therapies informed by such external control arm data while acknowledging the limitations of such data. In February 2023, natural history data was part of the totality of evidence used to approve Skyclarys (omaveloxolone) for treatment of Friedreich's ataxia.[9] Despite the two arms not having the exact same methodology and the natural history study not being "powered to detect a statistical difference between treatment groups in secondary endpoints," there was sufficient evidence for the FDA to approve the treatment.[10] Between 2010-2019, there were 45 instances where "pivotal studies" using external control data was accepted by the FDA for assessing benefits and risks of a treatment which was approved.[11] This includes Defitelio for hepatic veno-occlusive disease (a rare disease with a very high mortality rate and no previously available treatments), which was supported by data from multiple RWD sources. The historical control was not able to have an identical methodology—for example, the historical control had a longer time window for patient treatment—but the evidence was still acceptable for regulatory use.[12] These use cases represent a strong foundation to build upon as the research community continues to employ RWD to address practical and ethical dilemmas that traditional trial frameworks struggle to resolve.

Additional considerations

First, comment letters submitted in early 2022 requested that the FDA provide greater specificity and examples in future draft guidance documents, and we greatly appreciate the inclusion of more examples and use cases throughout this external control draft guidance document.

Although the present draft guidance considers summary-level estimates out of scope, it would be helpful for the FDA to define and discuss, if possible, the potential regulatory value of summary-level estimates.

Additionally, we encourage the FDA to include hybrid control arms (e.g., use of RWD to supplement concurrent trial control) in the scope of this guidance. The design, data, and analysis considerations are also relevant for such an approach and there are instances where supplementing a small control arm is necessary to assess the objectives in a study (e.g., rare diseases or vulnerable populations).

Though this guidance provides much useful information, there remain questions among stakeholders about how to determine whether an external control might be appropriate as part of an evidence package submitted to the FDA. Perhaps the agency can consider including at least one external control using RWD as part of the Advancing RWE Pilot Program use case to further highlight important considerations. Generally, earlier, more direct, and publicly available feedback on how RWE was considered in the FDA's decision-making process on any given application would be helpful. More significant insight into when RWE is substantial, secondary, or not considered for approval would allow stakeholders to better understand FDA thinking. The learnings will lead to submissions more in line with the agency's expectations as those expectations progress. As detailed throughout this comment letter, stakeholders are exploring ways to provide earlier and more comprehensive information in line with the

[9] Marcus, "FDA Widens Path for Rare-Disease Treatments With New Approval."
[10] Lynch et al., "Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study)."
[11] Jahanshahi et al., "The Use of External Controls in FDA Regulatory Decision Making."
[12] Richardson et al., "Phase 3 Trial of Defibrotide for the Treatment of Severe Veno-Occlusive Disease and Multi-Organ Failure."

FDA's guidance. This agency feedback would be an appreciated addition to early engagements with the FDA.

We appreciate the references to other RWE draft guidance documents in this latest document. As the body of guidance on RWE from the FDA grows, there will be increasing need for clear throughlines between the documents so that stakeholders can see how the different considerations fit together.

The broader stakeholder community should additionally develop resources reviewing the relative strengths and limitations of available approaches for assessing the potential impact of measured and unmeasured confounding. It is unclear in current FDA guidance whether available sensitivity and quantitative bias analysis methods would allay FDA concerns about unmeasured confounding. Furthermore, we ask the FDA to consider expanding the guidance to include the potential role of target trial emulation approaches for mitigating the bias issues discussed in the guidance document, including immortal time bias mitigation.

As the FDA continues to release and update RWE guidance, Duke-Margolis looks forward to continuing the advancement of RWD and RWE. We thank the FDA again for the opportunity to offer comments on this draft guidance. Please send any follow-up questions to Rachele Hendricks-Sturrup at rachele.hendricks.sturrup@duke.edu.

Sincerely,

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Appendix I

The following section lists the Real-World Evidence Collaborative's Advisory Group representatives and their respective member organizations as of May 1, 2023.

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