

May 2, 2023

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

Re: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products; Draft Guidance for Industry; Availability (Docket No. FDA-2022-D-2983)

To the Food and Drug Administration:

The RWE Alliance appreciates the opportunity to comment on the draft guidance entitled “Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products” (“Draft Guidance”).¹ We are a coalition of real-world data (“RWD”) and analytics organizations with a common interest in harnessing the power of real-world evidence (“RWE”) to inform regulatory decision-making to improve patients’ lives. Our members have deep knowledge and experience working with healthcare data across disease areas and patient populations, and we aim to bring these collective insights to bear in support of RWE policies.²

The RWE Alliance envisions a future in which data generated in everyday clinical practice and everyday life through electronic health records (“EHRs”), administrative claims and billing data, product and disease registries, personal devices, wearables, and health applications will be used to generate evidence that complements clinical trial data to inform regulatory decisions. To achieve this goal, the RWE Alliance advocates for policies that will (1) advance FDA’s RWE Framework, (2) encourage the use of RWE to better understand treatment effects in underrepresented populations, (3) enhance opportunities for RWE organizations to consult with FDA, and (4) increase communication on the generation and use of RWE.³

We appreciate FDA’s (the “Agency’s”) issuance of the Draft Guidance as part of the Agency’s RWE Program, consistent with its mandate under the 21st Century Cures Act.

¹ 88 Fed. Reg. 6748 (Feb. 1, 2023).

² For information about our members, please see our website, <https://rwealliance.org/who-we-are/>.

³ Additional information about what we believe is available on our website, <https://rwealliance.org/what-we-believe/>.

We also appreciate that the Draft Guidance recognizes that RWD can serve as a data source for externally controlled trials (“ECTs”). Section I of this letter provides our general comments on the Draft Guidance; Section II highlights comments on specific regulatory topics discussed in the Draft Guidance; and Section III discusses additional comments and clarifications.

I. General Comments on the Draft Guidance

A. FDA should highlight the circumstances in which using an ECT may be appropriate and useful for FDA decision-making.

The Draft Guidance explains that when “properly conducted, a clinical trial—with random assignment of participants either to a treatment arm or to a placebo (or other control) arm—optimally promotes the similarity of compared groups regarding such influences, such that a conclusion can be made as to whether differences in outcomes observed between groups can be attributed to the treatment of interest.”⁴ It notes that, “when appropriate,” a clinical trial using a non-randomized control can serve as an “adequate and well-controlled clinical investigation generally required to provide substantial evidence of effectiveness under section 505(d) of the Federal Food, Drug, and Cosmetic Act” (“FD&C Act”).⁵

We appreciate FDA's acknowledgement that a trial using an external control, including an external control based on RWD/E, can provide substantial evidence of effectiveness.⁶ We recommend acknowledging that RWD/E also can provide supportive evidence even when they do not provide substantial evidence of effectiveness. As such, we recommend clarifying—in the final guidance or in another guidance on the use of RWD/E—whether FDA's expectations may vary depending on whether the RWE-based evidence is intended to provide substantial evidence of effectiveness or support the totality of evidence in another way (e.g., supportive evidence or contextualization of safety information).

Overall, we support policies that help ensure any evidence relied upon by FDA in decision-making meets the high standards of the FD&C Act and FDA's implementing regulations. In the final guidance, it would benefit researchers if FDA further highlights the value that external control arms (“ECAs”) can bring to drug development and FDA review (e.g., highlighting various use cases or referencing literature where opportunities for ECAs have been discussed). We note that the Draft Guidance primarily outlines the challenges with use of ECAs, whether those ECAs are based on RWE or otherwise, and could do more to provide concrete recommendations for sponsors to address those

⁴ Draft Guidance at Lines 51–55.

⁵ Draft Guidance at Lines 57–60.

⁶ *Id.* The final guidance should consider referencing FDA's draft guidance “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.”

challenges.⁷ ECAs can offer an important alternative to generate evidence of effectiveness for serious conditions with significant public health needs or for rare disease indications with small patient populations that cannot be studied using a randomized design. Use of RWD also can contribute to increased efficiency compared to the timeline needed to carry out randomized controlled trials (“RCTs”). In sum, FDA should provide additional details on the appropriate use of ECTs to better unlock their full potential.⁸

II. Comments on Specific Sections of the Draft Guidance

The following subsections provide our comments on specific sections of the Draft Guidance. For ease of reference, the headings for each subsection correspond to the titles used in the Draft Guidance.

A. Design Considerations

1. Overview

The Draft Guidance states that sponsors “should finalize a study protocol before initiating the externally controlled trial, including selection of the external control arm and analytic approach.”⁹ Based on our experience, the final guidance should emphasize how the work of assessing the feasibility of RWD sources and designing an ECT protocol, which includes both the experimental arm and the ECA, should proceed as an iterative process, so that insights gained through data assessment can inform the study design (e.g., eligibility criteria, outcomes) and vice versa, with interactions between the sponsor and FDA at various stages, as needed.

We next suggest FDA explain details of footnote 18 in the main text of the final guidance, rather than in a footnote, given the importance of considerations about access to and evaluation of data sources and a trial’s feasibility.¹⁰

⁷ FDA should consider adding examples similar to those in the draft guidance “Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI-ML)-Enabled Device Software Functions,” in which the Center for Biologics Evaluation and Research, Center for Drug Evaluation and Research, Center for Devices and Radiological Health, and Office of Combination Products in the Office of the Commissioner illustrated different scenarios where a Predetermined Change Control Plan could be employed.

⁸ We recommend FDA consider citing Mishra-Kalyani PS, et al. External control arms in oncology: Current use and future directions. *Ann Oncol.* 2022 Apr;33(4):376-383. FDA should consider highlighting instances when ECTs may be considered with reference to additional literature.

⁹ Draft Guidance at Lines 106–107.

¹⁰ Draft Guidance at Page 4, Footnote 18.

Finally, we agree with the Draft Guidance that the “estimand framework . . . can be used to help design an externally controlled trial.”¹¹ We suggest FDA provide additional details on how sponsors can leverage the estimand framework and in which circumstances (e.g., whether the clinical questions of interest and associated estimands should be specified at the initial stages of planning any clinical trial).

We also suggest that FDA mention use of Target Trial Emulation methods along with the estimand framework. The estimand framework outlined in ICH E9(R1) provides a detailed view of how to describe “what” is the analytical goal of the clinical study with a primary focus on confirmatory clinical trials.¹² The guidelines implicitly employ counterfactual reasoning and acknowledge that the framework also can be applied to observational studies but do not describe the methods, conditions, or assumptions necessary to achieve this objective.¹³ Target Trial Emulation provides the detailed view of “how” to achieve the goal of the clinical study and estimand framework for observational study designs.¹⁴ That is, emulating a target trial is how one specifies an estimand within an observational study design. Given the recentness of E9(R1) and the time necessary to publish peer-reviewed papers, examples of authors making the explicit link between Target Trial Emulation and the estimand framework are only starting to emerge in literature.¹⁵ There are clear conceptual links between the estimand framework and Target Trial Emulation. Thus, we recommend the final guidance incorporate references to Target Trial Emulation as a way to make the relationship to the estimand framework clear and also to point readers in the direction of additional resources related to the “how” of implementing these frameworks in both experimental and observational study settings.

2. Characteristics of Study Populations

We agree with FDA’s statement in the Draft Guidance that a specific consideration involves aligning eligibility criteria to obtain a population comparable to the treatment

¹¹ Draft Guidance at Lines 114–116.

¹² FDA, E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials: Guidance for Industry (2021).

¹³ *Id.*

¹⁴ Rubin D. Estimating causal effects of treatments in experimental and observational studies. *ETS Res Bull Series*. 1972;1972:1–31; Hernán MA, Robins JM. *Causal Inference: What If*. Boca Raton, FL: Chapman & Hall/CRC 2020.

¹⁵ Akacha M, Bartels C, Bornkamp B, et al. Estimands-What they are and why they are important for pharmacometricians. *CPT Pharmacometrics Syst Pharmacol*. 2021 Apr;10(4):279–282; Hampson LV, Chu J, Zia A, et al. Combining the target trial and estimand frameworks to define the causal estimand: An application using real-world data to contextualize a single-arm trial. *Stat Biopharm Res*. 2023, DOI: [10.1080/19466315.2023.2190931](https://doi.org/10.1080/19466315.2023.2190931); Polito L, Liang Q, Pal N, Mpofo P, Sawas A, et al. Applying the Estimand and Target Trial frameworks to external control analyses using observational data: A case study in the solid tumor setting. <https://doi.org/10.48550/arXiv.2208.06707> (submitted Aug. 13, 2022).

arm. We suggest clarifying that the inclusion and exclusion criteria most important for alignment between the treatment arm and ECA are those criteria known or suspected to be associated with disease outcomes.

3. Attributes of Treatment

The Draft Guidance states that “[c]linical trial protocols typically include a plan for collecting data on use of concomitant or supportive therapies . . . that could affect the outcomes of interest,” whereas “documentation of such data in routine clinical care may not be complete or accurate, and RWD may therefore lack comprehensive details” describing such data.¹⁶ This statement appears more applicable to secondary analysis of RWD. We suggest that, as a general point toward the beginning of the final guidance, FDA acknowledge that primary data collection is one option that may help resolve some potential issues experienced when using secondary data.

4. Designation of Index Date (Time Zero)

We appreciate that FDA acknowledges the importance of considering how to assign the index dates within an ECA. To ensure sponsors are able to understand FDA’s expectations on how to assign index dates, we suggest the final guidance include examples.

Where patients in the comparator arm can be considered eligible at multiple time-points and/or treatment initiation and time zero do not coincide, recent methods such as the Target Trial Emulation framework and the “clone-censor-weight” approach have proven to be useful to obtain unbiased estimates in observational settings.¹⁷ These methods also can assist in the design and analysis of ECTs, with adaptations. We request that FDA clarify that design strategies or such statistical methods can be implemented to mitigate risk of bias.

5. Assessment of Outcomes

The Draft Guidance states that “lack of blinding to treatments in externally controlled trials can pose challenges” such as bias that can affect the validity of the study.¹⁸ We agree and appreciate FDA’s examples of how bias can be introduced. However, methodological strategies to help adjust for potential biases due to the lack of blinding in

¹⁶ Draft Guidance at Lines 190–197.

¹⁷ Maringe C, et al. Reflection on modern methods: Trial emulation in the presence of immortal-time bias. Assessing the benefit of major surgery for elderly lung cancer patients using observational data. *Int J Epidemiol.* 2020 Oct 1;49(5):1719–1729; Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol.* 2016 Nov;79:70–75; Backenroth D. How to choose a time zero for patients in external control arms. *Pharm Stat.* 2021 Jul; 20(4):783–792.

¹⁸ Draft Guidance at Lines 258–261.

ECTs exist, and the final guidance should acknowledge these approaches. They can range from propensity score models to synthetic cohorts' formation using digital twins, and we anticipate these strategies will only advance, which the final guidance should acknowledge.

The Draft Guidance further states that “[w]ell-defined, reliable, and clinically meaningful outcomes that are typically used in randomized trials may be particularly difficult to ascertain and evaluate in an RWD source that is being considered for an externally controlled trial.”¹⁹ We understand this statement to be focused on the challenges of not having primary data collection, in particular with RWD sources that may be considered for an ECA. We suggest that FDA move footnote 27 into the main text and expand upon how registries, which may collect data at predetermined intervals, are one option to help mitigate FDA’s concerns. The final guidance should acknowledge that primary data collection may help improve outcome assessments in a real-world study design (e.g., where images are collected in a real-world study to supplement real-world assessments of response).

Referring to considerations for outcomes in ECTs, the Draft Guidance states that sponsors can “evaluate whether the availability and timing of outcome assessments are sufficient and comparable across both arms of the externally controlled trial for the research hypothesis being tested.”²⁰ Timings of measurements do not always need to be comparable across both arms. For example, different timings of progression assessments may be mitigated by using interval-censoring methods.²¹ We suggest the final guidance add in parentheses “(as assured either by design or via data analytic approaches)” after “comparable.”

The Draft Guidance also considers challenges associated with changing diagnostic criteria over time.²² Common data models (“CDMs”) can help address the issue of changing diagnostic criteria over time by standardizing how health data are represented and stored, regardless of the source or time period of the data. The final guidance should consider acknowledging that CDMs, when used in appropriate circumstances, can make it easier to compare and analyze health data from different sources and time periods.

B. Data Considerations for the External Control Arm

In describing the possible data sources for ECAs, the Draft Guidance does not expressly discuss the possibility of an ECA formed by prospective or intentionally

¹⁹ Draft Guidance at Lines 269–271.

²⁰ Draft Guidance at Lines 299–301.

²¹ Zhang Z, Sun J. Interval censoring. *Stat Methods Med Res.* 2010 Feb;19(1):53–70; Dugué AE, Pulido M, Chabaud S, Belin L, Gal J. How to deal with interval-censored data practically while assessing the progression-free survival: A step-by-step guide using SAS and R software. *Clin Cancer Res.* 2016 Dec 1;22(23):5629–5635.

²² Draft Guidance at Lines 303–312.

captured data, i.e., a non-intervention group enrolled for research and potentially prospectively followed with or without retrospective RWD incorporated. We request FDA consider adding non-interventional, prospective data collection as a distinct data consideration.

1. Data from Clinical Trials

We appreciate the Draft Guidance’s discussion of utilizing previously collected clinical trial data. The Draft Guidance states that one concern for bias is selection of an ECA from a completed trial whose outcomes are already known. It continues, “[t]his would be especially problematic if the results of the external control arm are inconsistent with prior experience.”²³ We request the final guidance explain what “inconsistent with prior experience” means and address how sponsors should evaluate results of an ECA against it. The final guidance should also explain what documentation is sufficient for such an analysis.

2. Data from RWD Sources

While missing data and misclassification of data can be a challenge in RWD, potentially leading to biased or unreliable results, methodological approaches to understanding and mitigating the impact of missing and misclassified data can be leveraged. For example, one approach is to use imputation methods to fill in missing data. When reviewed rigorously, imputation methods can help to reduce the impact of missing data on the validity of the study results. The imputation method should be evaluated by comparing imputed data to available data for the same patient. Another approach is to use sensitivity analyses to assess the robustness of the study results to potential sources of bias, including misclassification of data. Researchers can perform sensitivity analyses by adjusting the inclusion and exclusion criteria or by using different definitions for outcomes or exposures. By testing the sensitivity of the results to these changes, researchers can better understand the impact of misclassification on the validity of the results and identify potential sources of bias. To avoid loss of statistical power, researchers should avoid over-adjustment and report methods and results of the sensitivity analysis transparently. We appreciate FDA acknowledging that imputation methods and sensitivity analyses are important tools to overcome missing and misclassified RWD,²⁴ which can help to ensure the validity and reliability of study results in ECTs.

3. Considerations for Assessing Comparability of Data Across Trial Arms

We recommend the following adjustments to the Table:

²³ Draft Guidance at Lines 340–341.

²⁴ Draft Guidance at Lines 433–456.

First, we suggest adding a line to describe evaluation of Inclusion and Exclusion criteria and relevant definitions.

Second, under Prognosis, we suggest adding the word “relevant” before “prognostic indicators.”

Third, under Treatments, we request providing guidance for time-varying treatments and confounders and for addressing such issues when designing ECTs. Given that most therapies operate under time-varying structures, where some also interact with time-varying covariates, the final guidance should provide recommendations on how to manage this issue in the design and analysis of ECTs.

Fourth, under Intercurrent events, we suggest including an outcome in the design that takes into consideration changes in treatment or intercurrent events after the index date.

Fifth, under Outcome, we suggest changing the last sentence to: “In addition, sponsors should be able to apply the same criteria or validated alternatives for the evaluation and timing of outcome assessments across both arms of the externally controlled trial.” Using the same criteria for evaluation and timing of outcome assessments across both arms may be too restrictive, such as when an outcome assessment collected as RWD for the control arm has been shown to be a valid alternative to one envisioned for the treatment arm.

C. Analysis Considerations

1. General Considerations

The Draft Guidance states that “an a priori threshold could be set to determine whether the external control population has a statistical distribution of covariates that is similar to the treatment arm population after a balancing method, such as weighting, has been applied.”²⁵ The word “similar” oversimplifies a broader spectrum of baseline similarity (e.g., good, fair, or weak). We suggest the following revision: “For example, a priori rules could be set to classify the similarity of the statistical distribution of covariates in the external control population after a balancing method, such as weighting, has been applied.” In addition, we suggest the following revision for footnote 30: “FDA does not endorse a single approach for determining such rules. As one example, rules could be selected for standardized mean differences as a metric that summarizes the statistical distribution of important prognostic covariates.”

2. Missing Data

The Draft Guidance states, “Assumptions about missing data can be unverifiable and may be difficult to justify, in addition to other assumptions required for estimation of treatment effect in a non-randomized setting.”²⁶ We suggest the final guidance append

²⁵ Draft Guidance at Lines 419–421 (Footnote omitted).

²⁶ Draft Guidance at Lines 438–440.

the following to the end of the sentence: “though not using analytical methods for missing data handling may also require assumptions (validity of a complete case analysis).”

3. Misclassification of Available Data

We recommend FDA further explain the consequences of differential misclassification. We suggest FDA move the discussion in footnote 32 of the Draft Guidance to the main text and expand upon FDA’s thinking related to different probabilities of misclassification in ECAs.

4. Additional Analyses

We appreciate FDA including an explanation of additional analyses. That said, the final guidance should expand upon FDA’s expectations with sufficient detail and add considerations for quantitative bias analyses.

D. Considerations to Support Regulatory Review

1. Communication with FDA

We appreciate FDA’s willingness to meet with sponsors during the early phases of study design and protocol development. We suggest that the final guidance include a discussion of key topics to address and decisions to be made in these early phases, particularly in the context of addressing and overcoming any potential limitations associated with a particular external comparator. For example, critical features may be considered in the development of the study synopsis (including the development of inclusion and exclusion criteria), the planning of feasibility assessments for data sources, the selection of data sources, and the final protocol and analysis plan.

2. Access to Data and Documents

The Draft Guidance recommends that sponsors include patient-level data in their marketing applications or ensure that their contracts with data owners allow patient-level data to be provided to FDA. It further recommends that sponsors should ensure FDA has access to source documents and source data for the ECA as part of an inspection or by FDA request. The RWE Alliance commented on the topic of sharing patient-level data and accessing source documents and source data as part of its response to the December 2021 draft “Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Guidance for Industry.”²⁷ We reaffirm our prior comments and build upon them below.

²⁷ RWE Alliance, [Comments](#) on Draft Guidance on Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Guidance for Industry, Docket No. FDA-2021-D-1214-0023, at Pages 8–10 (Mar. 9, 2022).

The RWE Alliance understands and appreciates FDA's need to have confidence in the quality and integrity of source data and to have patient-level data submitted to the Agency when an ECT is used as substantial evidence to support regulatory approval. At the same time, in the absence of more detailed information about FDA's expectations around access to source documents and data when sponsors use ECTs for substantial evidence, as well as around acceptable approaches that can be leveraged to meet those expectations in the context of RWD, FDA's high-level reference to needing "access" to secondary data sources could have the unintended consequence of chilling use of valuable RWD. The RWE Alliance remains committed to working with FDA as the Agency advances policies to meet FDA's objectives and expectations.

In circumstances where submitting patient-level data to the Agency is appropriate, we encourage FDA to clarify that any patient-level data submitted to FDA from an RWD source would be de-identified patient-level data. The final guidance should reflect privacy considerations raised by the sharing of patient-level data and provide approaches to accessing patient-level data that otherwise cannot be shared with FDA (e.g., data from jurisdictions outside of the United States).

III. Additional Comments

The RWE Alliance offers the following additional comments and suggested clarifications on the Draft Guidance.

- The Draft Guidance states, "This guidance does not address other types of external controls, such as using summary-level estimates instead of patient-level data."²⁸ We appreciate FDA's efforts to comprehensively outline methodological considerations for patient-level RWD-based external controls and believe that researchers' application of the Draft Guidance would be aided by clarifying the distinction between a patient-level external control and a summary-level external control. The difference between patient- and summary-level controls is somewhat opaque given publicly available use cases. For example, the RWE-based approval of Prograf (tacrolimus) relied on a summary-level estimate, despite the fact that patient-level RWD was submitted as part of the application package. To provide clarification, we suggest the final guidance include a glossary definition for each type of external control.
- We welcome additional discussion on the characteristics that differentiate external controls from internal controls.
- The final guidance should clarify that FDA does not intend to preclude use of external controls different in both time and setting. The Draft Guidance states, "The external control arm can be a group of people, treated or untreated, from an earlier time (historical control), or it can be a group of people, treated or

²⁸ Draft Guidance at Lines 33–34.

untreated, during the same time period (concurrent control) but in another setting.”²⁹ To avoid the implication that an ECA cannot be a group of people from both an earlier time and in another setting, we recommend that the final guidance add “and setting” to the sentence “from an earlier time *and setting* (historical control).”

- The Draft Guidance states that it “does not discuss considerations for using external control data to supplement a control arm in a traditional randomized controlled clinical trial.”³⁰ We ask that FDA clarify whether it meant to say “external data” instead of “external control data.” Specifically, we ask that the final guidance clarify whether FDA is referring to research data (internal data) versus data generated by others (external data) or to participants in a trial (internal control) versus a sample of participants that is different in time and/or setting (external control).
- We encourage FDA to reference other guidances³¹ that explain why a “non-inferiority approach is not recommended using an externally controlled trial design.”³²
- The final guidance should mention unmet medical need and describe the way in which that consideration should be factored into the decision around the suitability of an ECA.
- We encourage FDA to include a glossary definition for the terms “externally controlled trial” and “external control arm.”
- We suggest the two following topics for discussion in future guidance: (1) development of standards specific to clinical outcome assessments intended for clinical care settings that would be acceptable for regulatory use and monitoring of concepts that are important to the patient over the disease lifecycle and (2) considerations for hybrid study designs (i.e., a small internal control augmented with RWD-based external control).

IV. Conclusion

The RWE Alliance appreciates the Agency’s commitment to advancing the use of RWD and RWE in regulatory decision-making. Thank you for considering these comments,

²⁹ Draft Guidance at Lines 20–22.

³⁰ Draft Guidance at Lines 36–38.

³¹ FDA’s draft guidance “Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products” and FDA’s guidance “Non-Inferiority Clinical Trials to Establish Effectiveness.”

³² Draft Guidance at Page 3, Footnote 14.

and please let us know if you have any questions. We welcome the opportunity to discuss further.

Best regards,
The RWE Alliance