May 2, 2023

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

Re: Docket No. FDA–2022-D-2983: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance on **Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products.**

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

GENERAL COMMENTS:

Scope:

There are multiple ways in which an external control may be used in a regulatory application, whether as the primary pivotal evidence or as supportive evidence. The draft guidance references FDA's view that an external control may function as the "adequate and well-controlled study", which falls under the primary pivotal evidence. However, it is unclear if many of the guidance's recommendations and expectations, such as submission of the statistical analysis plan (SAP) before the first patient is enrolled in the clinical study, are also intended to apply to situations where an external control is intended to provide supportive evidence, such as demonstration of contribution of components for a combination regimen. In such supportive instances, it may be appropriate for additional flexibility to be provided. Therefore, we recommend that these aspects of the scope are clarified in the final version of the guidance.

The scope of the draft guidance is rather narrow, excluding aggregate-level data as well as hybrid designs using external controls to augment a RCT. BIO believes that extension of the scope to cover summary-level data and hybrid designs would significantly increase the practical

utility of the guidance. In addition, since many considerations are common to leveraging external controls in a hybrid or externally controlled trial, similarities and any points of difference between these designs could be more effectively discussed in an overarching guidance. Similarly, it would also be valuable to know how study protocols using an external comparator should be prepared, and how these should be submitted to health authorities and IRBs. For example, for a single arm trial with an external control arm should the protocol and analysis for both arms be included in the same document. If the protocols are to be kept separate, how should they reference one another in the final analysis/comparison?

Data Access and FDA/Stakeholder Engagement

The draft guidance also highlights the issue around FDA access to patient level data if data owners are unwilling or unable to provide it, which has been a theme across the entire guidance series that will necessitate further stakeholder alignment.

The draft guidance states, "Sponsors should also ensure that FDA has access to source documents and source data for the external control arm as part of an FDA inspection or upon request." Often, de-identified data are shared between organizations to the extent permitted by privacy laws. In the case of EHR data, data are patient-level but de-identified. Sponsors do not have the ability to identify the patients and get further clinical information. We ask FDA to clarify that the submission of de-identified data for the external control arm meets the FDA's requirements for submissions and reference privacy regulations associated with using de-identified data for human subject research. Providing this information would be extremely helpful for registry holders, especially when the sponsor is not the registry holder, etc.

In the case of RWD, FDA has noted in multiple guidance documents that it expects agreements to be in place between the sponsor and data provider in order to give FDA access to source data in order to verify the accuracy and integrity of data. It would be helpful for FDA to explicitly state that these expectations apply only to data that are considered part of an adequate and well-controlled study and are intended to serve as substantial evidence of effectiveness. Furthermore, it would be helpful if the Agency could clarify their expectations for source data verification of RWD in the instance of an inspection (e.g., non-redacted vs. redacted EHR source data with identifiable information removed to protect patient privacy). We believe these issues merit further discussion (e.g., a public workshop) to ensure that all stakeholder views are heard and considered. BIO believes this issue to be a critical component for the advancement of RWE for regulatory decision-making and recommend further discussion by stakeholders (e.g. a public workshop).

Multiple Data Sources

The data considerations described throughout the document are discussed exclusively in the context of a single data source for the external control. However, an external control that is comprised of patient level data from multiple sources may be the preferred option in certain

situations (to achieve target sample size or to enrich the data available on each patient through data linkages, etc.), provided that heterogeneity between the data sources is minimized. Therefore, we recommend that the Agency's considerations for an external control that is comprised of data from multiple sources be described.

The draft guidance generally assumes a single-arm trial protocol is unalterable and the comparator arm must be retrofit to the trial design. We acknowledge this issue in some programs, but request that FDA promote via the guidance co-development of single-arm trial protocol and RWE comparator arm protocol to harmonize data collection and support the integration of the totality of evidence being generated.

The guidance also provides limited information on summary statistics versus individual matched patient comparators. It would be helpful for the Agency to discuss what additional considerations or mitigations are acceptable in the design or analysis when intending to use summary measures for the primary comparison.

Ethical Considerations for RCT trial design

The guidance does not address the challenges of conducting randomized studies when there is an available therapy and the advantage of having data coming from the real-world while traditional RCT is not a viable option. Additionally, FDA may consider highlighting the issue of recruitment challenges for placebo-controlled trials in the setting of rare diseases with small patient populations and add consideration for facilitating science-based and patient-centric use of external controls.

The guidance should discuss the patient perspective, incorporation of patient voice into the trial design, concerns of patients with entering into placebo-controlled trials, considerations for pediatric trial and unwillingness and concerns of parents and caregiver with enrollment in placebo-controlled trials, etc.

The guidance states, "Externally controlled trials can be useful when it would not be feasible or ethical to use an internal control in the study, such as in studies of populations with rare diseases." However, while randomized clinical trials are considered the "gold standard," the guidance should also acknowledge ethical considerations for including rare disease patients in placebo controlled clinical trials. Use of externally controlled trials allows sponsors to minimize patient exposure to placebo and to reduce the number of patients and clinical trials needed for providing substantial evidence. Additionally, due to these ethical and moral concerns, many rare disease patients and caregivers are reluctant to participate in placebo-controlled trials. FDA should acknowledge the challenges of placebo control in development for rare diseases.

The guidance should also include a discussion of the evolving standard of care (SOC) and how the changing standard of care can make the placebo/SOC arm cumbersome in disease areas with evolving standard of care; coupled with desire of patients and health care providers (HCPs) to access the best available SOC.

Improving sponsors' familiarity with these terms and the underlying concepts can improve designs: 1) hypothetical target trial and 2) active comparator new user design.

Refer to Hernan et al., 2016, articles in sections describing design choices, particularly immortal time bias and how to avoid it (e.g., lines 229-242)[1,2].

Refer to Lund 2015 in sections describing biases and choice of index date (e.g., lines 244-254).[3]

Sensitivity Analyses to Address Residual Uncontrolled Confounding:

Reducing bias is a major theme in this guidance for designing externally controlled trials, but there can never be a guarantee the results are bias-free due to residual unmeasured or unobserved confounding, as suggested in Section III. C. 2. Missing Data. There are currently numerous methods to quantify this residual confounding, such as the e-value[4], array approach/rule-out methods[5], and many others[6,7,8]. We would recommend that the Agency comment on these types of methods for quantitative bias analysis and if/when they are warranted for inclusion in the study and pre-specified in the protocol. Given the variety of methods that have more recently been developed, a clear and recommended approach would avoid unnecessary convolution in the analysis plan, especially when considering a multitude of sensitivity analyses.

Index date:

The draft guidance proposes anchoring the index date at the occurrence of an eligibility diagnosis rather than the start of exposure to increase the comparability of clinical trial participants and (untreated) external controls. However, while we agree with the Agency's concern over immortal time bias, we disagree with the proposed solution. We suggest modifying the draft guidance to cite existing methods for mitigating immortal time in this setting which are less drastic than anchoring the analysis away from time of treatment initiation.

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[1] Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8):758-764.

[2] 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;79:70-75.

[3] Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep.* 2015;2(4):221-228.

[4] VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med*. 2017 Aug 15;167(4):268-274. doi: 10.7326/M16-2607. Epub 2017 Jul 11. PMID: 28693043

[5] Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Saf*. 2006 May;15(5):291-303. doi: 10.1002/pds.1200. PMID: 16447304.

[6] Zhang, X., Faries, D. E., Li, H., Stamey, J. D., & Imbens, G. W. Addressing unmeasured confounding in comparative observational research. *Pharmacoepidemiology and drug safety*. 2018; 27(4), 373-382.

[7] Zhang, X., Faries, D. E., Li, H., Stamey, J. D., & Imbens, G. W. Addressing unmeasured confounding in comparative observational research. *Pharmacoepidemiology and drug safety*. 2018; 27(4), 373-382.

[8] Uddin, M. J., Groenwold, R. H., Ali, M. S., de Boer, A., Roes, K. C., Chowdhury, M. A., & Klungel, O. H. Methods to control for unmeasured confounding in pharmacoepidemiology: an overview. *International journal of clinical pharmacy*. 2016; 38(3): 714-723.

Target trial emulation:

We suggest expanding the draft guidance to consider target trial emulation as a tool to inform the design and analysis of an externally controlled trial. Emulating a target trial is one of the main tools of causal inference and makes our goal of emulating a (hypothetical) randomized trial explicit. Discussion of target trial emulation will improve the design of externally controlled trials by providing sponsors with a tool with which to eliminate or mitigate design-associated biases. It will also facilitate a more transparent discussion of potential biases between the sponsor and the Agency.

Prospective Data Collection

The utility of prospective and intentionally captured RWD vs retrospectively collected RWD are not well differentiated in the guidance. FDA notes limitations of external controls using RWD that are relevant to retrospective RWD. Many of these concerns may be addressed through prospective intentional data capture. It would be helpful to note this in the guidance, as it highlights the need to identify fit-for-purpose data. We recommend that FDA consider making this point in future versions of this guidance.

The guidance states, "… whenever possible and for suitable endpoints, the outcome should be assessed blinded to treatment status." It is almost impossible in a fully historically controlled trial for the person entering the data on endpoints to not be aware that a patient has a particular disease and/or not know what treatment the person is on; therefore, the guidance appears to be guiding sponsors towards prospective data collection. In some cases, this activity may require re-adjudication of the externally controlled data, such as by blinded independent central review." The Agency should provide more information for requirements regarding the "Blinded Independent Central Review" as it is unclear what it means in a RWD setting and especially for historical records.

Additional Considerations:

This guidance is very thorough in terms of the key methodologic challenges and limitations of external comparator arms. However, it reads less as "recommendations" and more as reasons why an external comparator arm might not be accepted. What would be helpful to add to this guidance would be a section summarizing in what situations (at a high-level) external comparators may be more likely to be successful or can be considered. Mentions of this are scattered throughout the document, but BIO recommends a specific section that sponsors can go to for guidance when trying to make an initial decision on whether or not an external comparator arm might be worth further pursuing (e.g., when the effect size is expected to be large, when it is infeasible or not ethical to conduct a placebo arm in the clinical trial, when the outcome is an objective endpoint that is well-captured in real-world data). FDA should provide examples of the circumstances where the agency has accepted the effectiveness of a drug with an external control.

Overall, the points raised in the draft guidance are valid and helpful to designing and implementing externally controlled clinical trials. This guidance document is very timely to provide guidance regarding the use of historic trial and/or RWD to provide evidence of safety and effectiveness of a drug product. However, there is some significant gap of potential ECA approaches to improve the efficiency of drug development such as digital twin, hybrid ECA (randomized control + ECA control). Additional guidance on these topics is welcome and/or views on where considerations for ECAs in this guidance do apply also to hybrid control designs.

BIO applauds FDA for thinking broadly and including in the guidance both external clinical trials but also the option of external data from real-world data (RWD) sources, such as registries as well as electronic health records (EHRs) and medical claims data. While the draft guidance presents many of the common challenges in conducting externally controlled trials, it does little to present actionable solutions or ways to mitigate those challenges. The guidance does an excellent job at specifying how high the bar is for the externally controlled studies and while we acknowledge that no single externally controlled study is the same, it is still necessary to provide a discussion of actionable solutions that are case specific by way of examples. We believe the challenges outlined should be accompanied by recommendations to overcome these challenges, examples of how similar or identical challenges have been successfully overcome, and clear articulation of regulatory flexibility FDA intends to use to mitigate or eliminate some of these challenges.

Sincerely,

/s/

Camelia Thompson, Ph.D.
Senior Director, Science and Regulatory Policy
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Title, Page 2, Lines 33-38	**Title:** 'Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products' The authors state the scope of this document on **page 2, lines 33-38**: 'This guidance does not address other types of external controls, such as using summary-level estimates instead of patient-level data. This guidance does not discuss details of the design and analysis of a natural history study nor the reliability and relevance of various sources of RWD that could be used in an externally controlled trial. Finally, this guidance also does not discuss considerations for using external control data to supplement a control arm in a traditional randomized controlled clinical trial.' The title does not match the more specific scope of the document's contents. If additional guidance documents on external controls follow in the future, it would be helpful to know from the title of each document the scope of each document's contents.	**BIO suggests the following edit to the title to better describe the contents**: 'Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, **Using Patient-Level Data from Clinical Trials or Real-World Data Sources**,'

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	It is not clear whether "use of external control data to supplement a control arm" refers to (1) use of RWD to supplement CT data; or (2) adding an additional extra control data in a trial that already has a control arm. If the latter, aren't the considerations discussed in this document largely applicable to the scenario? When/where will this concept be addressed if not in this guidance?	
Section	The draft guidance focuses largely on the challenges and potential biases in using external controls without emphasizing the advantages. Including a statement in the introduction or background would be helpful to contextualize why a sponsor might conduct external controlled trials.	BIO recommends the following addition to the introduction or background section to help contextualize why a sponsor might conduct external controlled trials: "**External controlled trials may require a smaller sample size compared to a randomized controlled trial. This may be helpful to expedite drug development and may make clinical trials possible in serious or rare diseases, where there may be ethical concerns in use of placebo control."**
Page 1, line 17	FDA should consider the value of externally controlled studies when evaluating effectiveness and safety in an RCT is not feasible, and how such studies may inform benefit/risk decisions as part of the totality of evidence as supporting information. Externally controlled studies may not necessarily meet FDA's evidentiary standards on their own but could still be used to contextualize results of a clinical trial. This is	BIO recommends the Agency provide clarification on how externally controlled studies may contribute to benefit/risk decisions.

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	especially true for rare diseases, considering the limited data availability in general	
Section 1 overview	The guidance does not explicitly state whether it should be applied to both exploratory and confirmatory studies. There is also no mention of considerations that might be specific to externally controlled trials conducted in rare diseases or pediatrics.	BIO recommends that the Agency clarify in Section I whether the guidance is intended to apply to confirmatory trials and/or exploratory trials. It would also be helpful to reference the draft ICH E11A guidance on pediatric trials, which discusses externally controlled trials and use of external information to augment RCTs.
Line 22	The draft guidance states, "…during the same time period (concurrent control) but in another setting." It may be better to use the label "concurrent external control" rather than "concurrent control" to avoid any confusion with the use of this phrase in platform trials. The definition of historical control (from an earlier time) and concurrent control (during the same time period) are overly simplified and inconsistent with ICH E10 and 21 CFR 314,126(b). A trial could expand across multiple years. How much overlapping time is needed to be qualified as concurrent control?	BIO recommends that the Agency consider using the label "concurrent external control" rather than "concurrent control" to avoid any confusion with the use of this phrase in platform trials. BIO recommends the Agency use consistent language for historical control and concurrent control with ICH E10 and 21 CFR 314.126(b).
Page 2, Lines 27-29 and general comment	The draft guidance states, "… this guidance focuses on the use of patient-level data from other clinical trials or	BIO recommends that the Agency ensure that the language throughout the guidance is broad enough to accommodate the full range of data sources that could provide external controls, including primary-use RWD such as prospective registry studies

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	from real-world data sources, such as registries as well as electronic health records and medical claims". This initial text is broad enough to encompass patient-level external controls drawn from primary-use or secondary-use RWD. However, this language is not carried forward to the rest of the document (see, for example, Page 4, Footnote 18, where the current wording seems to implicitly assume external controls will be drawn from secondary-use RWD.) When no existing relevant data are available on control, but a RCT is infeasible or unethical, a sponsor may need to plan to prospectively generate RWD on control for an externally controlled trial, e.g. via a prospective registry study.	designed to run concurrently with the externally controlled trial.
Page 2, Line 27-29	The draft guidance states, "... this guidance focuses on the use of patient-level data from other clinical trials or from real-world data (RWD) sources, such as registries as well as electronic health records (EHRs) and medical claims." The Agency should clarify that this allows for using data at earlier time points (e.g. from interim analysis), especially in the case where an external control are from a platform trial	BIO recommends the following edit: "... this guidance focuses on the use of patient-level data from other **ongoing or completed** clinical trials **(including master protocols)** or from real-world data (RWD) sources, such as registries as well as electronic health records (EHRs) and medical claims.
Lines 33-36	Hybrid trial designs, which may incorporate pragmatic or decentralized elements, and the use of external	Generally, the same design and analysis considerations are common to both external controls and hybrid studies.

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	control data to supplement a control arm in a RCT are excluded from guidance.	Additionally, many of the considerations are similar when using external control data to supplement a randomized control arm. BIO recommends incorporating additional elements of these studies into this guidance. We acknowledge some of these studies may be the scope of another upcoming guidance, *Using Clinical Practice Data in Randomized Controlled Trials (RCT) for Regulatory Decision-Making for Drug and Biological Products.*
Page 2 Lines 33-34	The draft guidance states, "…does not address other types of external controls, such as using summary-level estimates instead of patient-level data". However, aggregate data on control may be regarded as highly relevant information and, if identified according to a systematic and pre-specified search strategy, may be just as reliable as individual patient data drawn from RWD. In cases where standard of care is stable and has been used as the comparator in published historical RCTs, even if patient-level data cannot be accessed from these studies, the aggregate data may be considered a source of highly relevant and reliable information. We note there may be scenarios where sponsors may not have direct access to patient level data, or the transfer of data is restricted due to national/local data protection regulations. Sponsors can provide the analysis plan and share the results of the analysis or reports from a third party.	BIO recommends the Agency consider expanding the current guidance (particularly Section B.1) to include discussion of the use of aggregate data on control, particularly from relevant historical RCTs. Specifically, consider including more detail about mechanisms that may be used to make patient-level data available to FDA directly from data holders.

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Lines 36-38	The draft guidance states, "Finally, this guidance also does not discuss considerations for using external control data to supplement a control arm in a traditional randomized controlled clinical trial." However, hybrid approaches (using trial-external controls to augment the control arm of a RCT with imbalanced allocation between arms) represent an important class of design which in many settings may be preferred to an externally controlled trial. This is because when following a hybrid design, one can directly verify the comparability of trial-internal and external controls using baseline covariate and outcome data, and dynamically determine the weight that should be attributed to the external controls according to pre-specified statistical approaches. The narrow scope of this guidance is a missed opportunity. We would appreciate a discussion about summary-level external controls arms in this guidance. Similarly, the guidance should also include the use of external controls to augment traditional RCTs, as this approach has been recommended by the Agency in publications and presentations. Many design and analytic considerations are common to leveraging external controls in a hybrid study or externally controlled trial.	BIO recommends that the Agency consider clarifying where a sponsor should submit a formal external control arm vs. data to supplement a control arm. BIO also recommends that this topic is discussed in upcoming guidance or as part of the final version of this draft guidance. BIO recommends the Agency extend the current guidance to also discuss hybrid trials using external control data to augment the control arm of a RCT.

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	Using patient-level external controls to supplement concurrent controls has unique advantages such as the ability to adjust bias due to systematic difference between trial setting and real-world clinical practice settings. Besides, lots of considerations stated in the draft guidance would apply to the partial external control supplementation scenario as well. Therefore, we believe adding discussions on this design would add necessary clarifications to sponsors, to help them choose the most appropriate alternative design.	
Footnote 7	The draft guidance states: "Given that an external control arm can involve the use of RWD, FDA is issuing this guidance to satisfy, in part, the requirements of the 21st Century Cures Act to issue guidance on the use of real-world evidence (RWE) in regulatory decision-making, specifically to evaluate the potential use of RWE to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy postapproval study requirements." BIO recognizes the language in footnote 7 from other RWD guidance documents; however, we acknowledge that external controls are commonly used for	BIO recommends the following revision to the footnote: "Given that an external control arm can involve the use of RWD, FDA is issuing this guidance to satisfy, in part, the requirements of the 21st Century Cures Act to issue guidance on the use of real-world evidence (RWE) in regulatory decision-making, specifically to evaluate the potential use of RWE to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy postapproval study requirements. **External controls may also be used during the development of an unapproved drug."**

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	unapproved products and should be clarified in the footnote or elsewhere in the guidance.	
II. BACKGROUND		
Line 51	The clause "When properly conducted…" suggests that a clinical trial is only properly conducted when it includes random assignment to treatment or control, which goes against the point of the guidance that external controls may be reasonable.	BIO recommends the following edit: ~~"When properly conducted~~ **A Randomized controlled** trial – with random assignment …."
Line 51-55	It is unclear whether anytime randomization is not implemented, any control will be considered external control.	BIO recommends that the Agency specify that external control is discussed in this guidance document.
Page 3, lines 57-60 and footnote 14	It is unclear whether the scope of the guidance is on using external control to establish effectiveness/efficacy and not on evaluation of safety (e.g., to rule out risk). It is also unclear whether the guidance stated applies to evaluation of safety with an active control drug and ruling out risk using an external control to inform benefit-risk evaluations It is good to see acknowledgement that other types of control arms can, when appropriate, serve as adequate and well-controlled clinical investigations.	BIO recommends the Agency clarify the scope of the guidance.
Lines 57-60	The draft guidance states, "Clinical trials using these other types of controls can, when appropriate, serve as the adequate and well-controlled clinical investigations generally required to provide substantial evidence of	BIO recommends that the Agency consider clarifying their consideration of the rare disease situation in which there are so few patients, that often this may be one of the few days to conduct the study and still have a comparison group.

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	effectiveness under section 505(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)." This is very helpful. The Agency should share if any thought been given here to the rare disease situation in which there are so few patients, that often this may be one of the few days to conduct the study and still have a comparison group.	
Lines 62-68	The draft guidance states, "Given that externally controlled trials do not involve randomization of the study population to the treatments being compared, the treatment and control arm populations should be as similar as possible regarding known factors that can affect the outcome being measured. These factors, discussed in more detail in section III, include important baseline characteristics (e.g., demographic factors, comorbidities), disease attributes (e.g., severity, symptoms, duration of illness), start of follow-up for the treatment of interest, concomitant therapies, and the clinical observations collected." Concomitant therapies do not always need to be similar between treatment and control arm since their use can be affected by the test/control treatment. Precisely defining treatment condition of interest is of great importance.	BIO recommends that the Agency consider the following edit: "Given that externally controlled trials do not involve randomization of the study population to the treatments being compared, the treatment and control arm populations should be as similar as possible regarding known factors that can affect the outcome being measured. These factors, discussed in more detail in section III, **may** include important baseline characteristics (e.g., demographic factors, comorbidities), disease attributes (e.g., severity, symptoms, duration of illness), start of follow-up for the treatment of interest, concomitant therapies, and the clinical observations collected."
Lines 66	Degree of pre-treatment/line of therapy is important for oncology, but directionally also for benign diseases. Please add to the examples given to characterize	BIO recommends that the Agency add to the examples given to characterize comparability of disease settings for external control and single arm study population.

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	comparability of disease settings for external control and single arm study population.	
Line 67	The draft guidance states, "…start of follow-up for the treatment of interest…"	In addition to "start of follow-up for the treatment of interest", BIO suggests adding duration/length of follow-up for the treatment of interest.
Line 73	The draft guidance states, "The suitability of an externally controlled trial design warrants a case-by-case assessment…" This can open up the potential imbalance for how the agency divisions review. This lack of standardization may be problematic.	The Agency should provide some level of standardization against which trial designs would be **considered appropriate**, and all review divisions and Centers (CDER, CBER, CDRH) should rely on the same criteria.
Lines 73-81	Original text: "The suitability of an externally controlled trial design warrants a case-by-case assessment, informed by issues including heterogeneity of the disease (e.g., clinical presentation, severity, prognosis), preliminary evidence regarding the drug product under investigation, the approach to ascertaining the outcome of interest, and whether the goal of the trial is to show superiority or non-inferiority. […]" Examples are listed when external controls are most appropriate, but some of the examples require further clarification in the guidance.	BIO requests the Agency provide more specifics and the current thinking around some of the examples provided (e.g., heterogeneity of disease, superiority vs inferiority) in this section or the following design section. For example, under what circumstances related to disease heterogeneity or superiority vs inferiority would lead the Agency to conclude on the suitability (or unsuitability) of an externally controlled trial design? BIO also recommends that the Agency specify whether this refers to preliminary evidence of the magnitude of effect of the drug product, adverse events of concern, or other relevant evidence.

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	The included factors may be important considerations regarding the suitability of externally controlled studies. In this kind of situation with a single arm trial (oncology trial with ORR endpoint), it is helpful to provide more details on the recommendations for setting up of objective threshold, and clarify whether/under what circumstances an external controlled arm is still needed.	We suggest expanding the list of issues that may factor **(bold text)** into an assessment of the suitability of an externally controlled study. " The suitability of an externally controlled trial design warrants a case-by-case assessment, informed by issues including the **features and/or** heterogeneity of the disease (e.g., clinical presentation, severity**,** prognosis), **availability of treatment (i.e. unmet medical needs), ethical considerations,** preliminary evidence regarding the drug product under investigation, **including whether the mechanism of action of the drug is related to the cause of the disease (i.e. targeted therapy),** the approach to ascertaining the outcome of interest, and whether the goal of the trial is to show superiority or non-inferiority."
Lines 77-79	Original text: "Of note, if the natural history of a disease is well-defined and the disease is known not to improve in the absence of an intervention or with available therapies, historical information can potentially serve as the control group." The term "historical information" is unclear. We assume that this term does not refer to natural history studies. Accordingly, we have provided edits to further clarify the term "historical information."	BIO recommends the following revision: "Of note, if the natural history of a disease is well-defined and the disease is known not to improve in the absence of an intervention or with available therapies, historical information **(e.g., existing data from other clinical trials or from RWD sources)** can potentially serve as the control group." While footnote 4 refers to previous FDA guidance on various types of controls, we recommend including examples with relevant considerations. BIO recommends the Agency expand the section on how a disease may be characterized as "well-defined" such as the

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	Use of concurrent vs. historical controls is discussed on lines 77-78. However, there is a limited discussion on considerations of each option including advantages and limitations when selecting one of these options for an external control	disease course is predictable and the pathophysiology is well understood.
Lines 77-88	It is unclear if this section is still considering patient-level data as specified in Section I. The historical information to derive the threshold for objective response rate is often from summary-level estimate.	BIO recommends that the Agency consider revising the example.
Lines 83-84	Original text: "In many situations, however, the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low, and sponsors should choose a more suitable design, regardless of the prevalence of disease." We believe that a well-designed study with an external control can effectively answer important research questions. It would be helpful if the guidance could acknowledge this by tempering the use of the word "many" in this sentence. Besides large effective size, please clarify if ECA can be used for B-R assessment in single arm study when randomization studies are not possible due to practical reasons in a patient population with highly unmet need but rare indication.	BIO recommends the following revision: "In ~~many~~ **some** situations, however, the likelihood of credibly demonstrating the effectiveness of a drug of interest with an external control is low, and sponsors should choose a more suitable design, regardless of the prevalence of disease." BIO recommends that the Agency clarify if ECA can be used for B-R assessment in single arm study when randomization studies are not possible due to practical reasons in patient population with highly unmet need but rare indication. BIO suggests FDA note how unmet medical need could potentially be factored into the decision on the suitability of an external control arm.

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	It is unclear whether FDA will consider an external control arm study only when a more suitable design is not feasible (for practical or ethical reasons), regardless of methodological acceptability.	
Footnote 17	It is unclear why, if the course of the disease is well understood but variable, external controls are inappropriate. If by variable refers to statistical variability, it should not be an impediment.	BIO recommends that the Agency define whether "variable" refers to statistical variability, non-statistical variability, or a combination of both.
III. DESIGN AND ANALYSIS OF EXTERNALLY CONTROLLED TRIALS		
A. Design Considerations		
1. Overview		
Entire Section		BIO recommends the Agency consider including additional details on the appropriate types of data the Agency would consider accepting.
General comment, **Section 1 overview and Section III.A**	The guidance implies rather than explicitly stating that the goal of the design and analyses are to emulate a randomized study comparison and maximize internal validity. In line with this, the current text on design considerations does not discuss target trial emulation. However, this is an established and structured approach to the design and analysis of a non-randomized study which aims to increase confidence in the robustness of causal inferences through emulation of the design and analysis of a (hypothetical) target randomized trial.	BIO suggests that it would be helpful for the Agency to state the goals of maximizing internal validity, mimicking a randomized design, and taking the clinical trial design as the benchmark upfront in the overview section. Furthermore, BIO also requests that the Agency consider expanding Section III.A.I to mention that target trial emulation can be applied in conjunction with the ICH E9(R1) framework. This would see sponsors first translate the estimand into the protocol of a hypothetical target randomized trial, and then specify the design and analysis plan of the externally controlled study to emulate the protocol of the target trial as closely as possible. Specification of the target trial would bring further

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	The use of target trial emulation is a structured approach that can help sponsors avoid or mitigate design associated biases (such as immortal time bias) through careful emulation of a randomized clinical trial. In addition, target trial emulation facilitates more transparent and granular discussions about potential sources of bias and their mitigation strategies. In particular, it allows sponsors to disentangle 'biases' into 'external biases' (arising because the external control data does not completely capture the population, treatment, variable and other intercurrent events attributes of the target estimand) and 'internal biases' (arising because limitations in the quality of the external control data mean estimates of the estimand of the externally controlled study are potentially biased).	clarity on what is to be considered as the "benchmark" when evaluating the comparability of the data sources. References: MA Hernán, JM Robins. *American Journal of Epidemiology* 2016; 183(8):758 MA Hernán. *New England Journal of Medicine* 2021;385;1345 See Hampson et al, 2022; Polito et al, 2021 for clinical studies using RWD which used the target trial and ICH E9(R1) frameworks in combination.
Lines 105-108	The draft guidance states, "Sponsors should finalize a study protocol before initiating the externally controlled trial, including selection of the external control arm and analytic approach, rather than selecting an external control arm after the completion of a single-arm trial." The phrasing here is a bit confusing – there are multiple study milestones mentioned for the external comparator and the single arm trial. It seems the suggestion is that that protocol needs to be finalized before the single-arm trial is completed, and before an external control is initiated.	BIO recommends that the Agency clarify as there are multiple study milestones mentioned for the external comparator and the single arm trial. BIO also recommends the following edits: "**The design and analytic approach of the external control arm should be part of the early planning process for the single-arm trial**. Sponsors should develop the single-arm trial protocol and external control arm study protocol concurrently."

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	Timing of the development of the external control arm is ideally concurrent with the development of the single-arm trial protocol. The design and analytic approach of the external control arm should be part of the planning process of the single arm trial rather than choosing the control arm after the completion of the single arm trial.	BIO also recommends that consideration be given to the fact that it is not always feasible to initiate a new externally controlled study when investigating rare and ultra-rare diseases, especially in pediatric patient populations and that on-going or existing studies may be the only source for an external control.
Page 4, Lines 105-108	BIO agrees that pre-specification of intent/purpose of using external control and how to use prior to data collection into the clinical trial would be ideal. Nevertheless, the treatment landscape in some therapeutic areas is dynamic and faster than the study completion. Thus, an acceptable single arm study today may not be sufficient when competitor products begin to be approved. A comparison to an external control remains an informative and timely option of informing a comparison to an active control arm.	BIO recommends the Agency consider rephrasing the section to emphasize that while the idea is pre-specification, that introducing, and discussion use of external control is still possible prior to unblinding/finalizing the clinical trial results.
Page 4, Line 110 and footnote 18 on Page 4	The elements recommended for inclusion in protocols are extensive. This may delay protocols and make them long, complicated, and highly technical. Estimand selection and language to explain methodology to balance groups and to minimize bias are not relevant for investigators and possibly not easy to understand.	BIO recommends that the Agency only require a high level approach for inclusion into the protocol and allow details to go into SAP.

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Footnote, 18	The draft guidance states, " Sponsors should provide a justification for selecting or excluding relevant data sources…" Footnote 18 is critical information that should be elevated to main body of the text.	BIO recommends that the Agency consider adding an appendix of justification examples both positive and negative to help facilitate choosing correct data sources. BIO recommends the Agency move Footnote 18 to the main text of the guidance.
Footnote, 18	Footnote 18 of Section III A. Design Considerations states, "FDA recommends that sponsors generate audit trails in their datasets that can track access to and analyses performed on relevant data sources". However, the audit trail in a clinical trial does not fully apply to the RWD sources and is further complicated by the same data source(s) that are used for feasibility and then for the full study execution as some assessment is first needed to demonstrate feasibility. The technical burden both on sponsors and on regulatory inspections of audit trails for RWD data sources are unrealistic and will not likely achieve the intended objectives. FDA recommends sponsors create an audit trail in datasets to track access/analyses performed on RWD. More specific guidance here would be helpful, as many RWD sources that would be used for an external comparator analysis may also be used for non-regulatory, internal RWD work. Having more detailed guidance on how to store/track usage of datasets used for regulatory external comparator studies, when to	BIO agrees that it is important to demonstrate transparency in the analyses and timing of such analyses when using RWD for externally controlled studies. BIO recommends that the agency provide recommendations on what an audit trail encompasses in the context of RWD and/or external clinical trial data that are used for externally controlled studies. For example, solutions may include documentation of individuals who can access the data, timing, and rationale. Additionally, the Agency should provide a clear distinction of the types of analyses to support feasibility vs. full study execution.

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	start this process, and how to document/communicate this so it is acceptable to FDA would be helpful.	
Page 4, Line 106-107	The draft guidance states, "Sponsors should finalize a study protocol before initiating the externally controlled trial, including selection of the external control arm and analytical approach …" The current wording seems to suggest that the patient-level external controls themselves should be selected before initiating the externally controlled trial. However, some common design approaches (e.g., propensity score matching) require data on baseline covariates for the single-arm trial participants to select the patient-level external controls. Additional clarity is needed regarding at what point in the externally controlled trial the analytic dataset for the control arm should be finalized.	BIO recommends the following edit: "Sponsors should finalize a study protocol before initiating the externally controlled trial, including **the data sources and process for identifying patient-level external controls** and analytical approach …"
Lines 106-112	It is unclear whether a protocol can be amended during the course of an externally controlled trial. Or, rather, which aspects of trial designs can be modified. An adequate and well-controlled trial may amend its protocol during the trial course per learning from the trial. It should be allowed to modify the externally controlled trial as long as scientific rigor is maintained.	BIO recommends that the Agency clarify whether a protocol can be modified during the trial.
Line 112	The draft guidance states, "…and approaches to minimize missing data and sources of bias."	BIO recommends that the Agency add pre-specification of confounders in the protocol as well.

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	In the design elements, the Agency should include confounding variables and covariates.	
Page 4, Line 112	This paragraph is focused on what is included in the protocol but a feasibility assessment is crucial before moving to the protocol stage. When historical data is used as the source for the external control, a feasibility analysis is recommended before finalizing the study protocol. The feasibility analysis can be useful to understand details of the data source, data integrity and limitations. Hence it helps to assess if the historical data is fit-for-use. Additional information may be found here. Reference: Fang J., Wirta SB., Kahler K. Secondary Use of Data: Non-Interventional Study Best Practices in Planning and Protocol Development. *Journal of Health Economics and Outcomes Research,* 2017, 5(1):27	BIO recommends that the Agency consider including information about feasibility studies that should occur before the protocol is developed.
Lines 114-120	The estimand framework can be used to help design an external control trial. However, one challenge in RWD is intercurrent events likely not recorded in the external data. Further guidance is needed whether and when the estimand framework is appropriate or feasible to be specified in the protocol and/or SAP (STATISTICAL ANALYSIS PLAN) of the external control trial.	BIO recommends the Agency consider providing some discussions or examples on whether and when to specify the estimand components and the strategy of handling missing data in the protocol and/or SAP (Statistical Analysis Plan) of the external control trial. A statement such as "the appropriateness of the estimand framework in this setting depends on data quality" may be worthwhile.

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Lines 126-128	The draft guidance states, "… a thorough understanding is needed – but is often difficult to verify – regarding the natural history …" Natural history of disease and prognostic factors are sometimes well known – characterizing them as "often difficult to verify" is inaccurate.	BIO recommends that the Agency clarify what is meant by 'often difficult to verify'.
Lines 132-134	Original text: "From a practical perspective, fit-for-use data on suspected confounding factors (e.g., history of cigarette smoking, performance status) may be missing for some patients or participants or may be measured differently in the external control arm compared to the treatment arm." The draft guidance document seems to be very focused on oncology. Although external controls are not used as often in the general medicine space, they have been used in the cases of rare (non-oncology) diseases. We suggest adding a confounding factor that is applicable beyond the oncology setting.	BIO recommends the following revision: "From a practical perspective, fit-for-use data on suspected confounding factors (e.g., history of cigarette smoking, performance status, **history of prior treatments**) may be missing for some patients or participants or may be measured differently in the external control arm compared to the treatment arm."
Lines 136-138	The draft guidance states, "…sponsors should confirm that recognized, important prognostic characteristics can be assessed…" In practice, the list of important prognostic factors may need to be listed by priority during the data source assessment to ensure that the more strongly prognostic	BIO recommends that the Agency clarify that the list of important prognostic factors may need to be listed by priority during the data source assessment to ensure that the more strongly prognostic factors are prioritized.

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	factors are prioritized. Clinical input either from within a market authorization holder (MAH) may suffice, or a steering committee may be recommended.	
Page 5, Line 138	The draft guidance states, "…used in an externally controlled trial. Specifically, the source population for the external control arm should be as comparable…" The Agency should consider including "feasibility analysis" as an example to confirm if the externally controlled trail is suitable. The reason for requesting such an edit is that if two or more different data sources are contributing to the external control, that fact can also have implications for the analysis methods	BIO recommends the following edit: "…used in an externally controlled trial **(e.g., performing a feasibility analysis).** Specifically, the source population**(s)** for the external control arm should be as comparable…"
Lines 138-141	The draft guidance states, "Specifically, the source population for the external control arm should be as comparable as possible to the treatment arm population, given that controlling for differences between the two study arms (see section III.C) becomes more challenging with increasingly dissimilar populations." The Agency should clarify if a Sponsor is considering an externally controlled trial, should the I/E criteria of the clinical trial experimental arm be loosened to permit better matching with the external control, provided that the criteria match with current US medical	BIO recommends the Agency clarify that if a Sponsor is considering an externally controlled trial, should the I/E criteria of the clinical trial experimental arm be loosened to permit better matching with the external control, provided that the criteria match with current US medical practice.

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	practice. This would appear to be consistent with the text in lines 390-392 as well.	
Lines 139-141	It may not be practical in some cases (e.g. rare diseases, indications with many prognostic factors, etc..) to ensure high level of comparability.	The Agency should clarify, in such cases, if the Agency would consider analytic approaches such as multivariate regressions, stratified comparisons) as acceptable remedies. Proposed additional text after line 141: **"Statistical approaches such as regression analysis or stratified comparisons should be used to address the imbalance when high level of comparability for all prognostic factors is impractical".**
Line 143-146	The draft guidance states that "Although unmeasured confounding, ... an assessment of the extent of confounding and bias, along with analytic methods to reduce the impact of such bias, are critically important in the conduct of such trials." BIO recommends that the Agency provide additional details on the assessments and/or analytic methods the Agency would recommend. It is unclear how the assessment of the extent of confounding and bias can be performed in the case of unmeasured confounding. More guidance regarding appropriate methods for measuring impact of unmeasured confounding would be helpful (e.g., simulation of a confounder at various strengths and its impact on effect estimate). Guidance reviewing the relative strengths and limitations of	BIO recommends that the Agency consider providing some examples of such methods, or reference to later sections where such methods might be mentioned. BIO recommends that Agency provide additional details on appropriate methods for measuring impact of unmeasured confounding.

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	available tools for assessing potential impact of measured and unmeasured confounders should be developed.	
Lines 146-148	It is challenging to define how large the effect size on a well-characterized outcome of interest is large enough to use external control. But when the effect size is large and clinically meaningful, using an external control may not add too much value in certain situations, especially for a disease which is well-understood, and the outcomes won't improve without treatment. It is not clear when to best use the external control. For example, in the FDA guidance for industry: Considerations for Allogeneic Pancreatic Islet Cell Products, the following is stated: "Evidence of clinical safety and efficacy for licensure is generally derived from prospective, randomized, controlled clinical trials. However, for the evaluation of allogeneic islet cell products, a single-arm, open-label trial may be able to provide substantial evidence of efficacy and safety in subjects with metabolically unstable Type 1 diabetes. In this design, a historical control arm may be used." A Sponsor would conclude that no externally controlled study is warranted. The large treatment effect can be relative to the sample size from a statistical point of view. Clarify if a	BIO recommends that the Agency clarify how large the effect size on a well-characterized outcome of interest needs to be to use an external control and discuss this in the context of minimum clinical important difference when it is available. In addition, it is helpful to clarify that using an external control could provide more value for a disease which is well-understood, and the outcomes become worsened or won't improve without treatment. BIO also recommends that the Agency specify how to determine whether the effect size is large.

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	large treatment effect refers to a clinically large treatment effect exclusively.	
Line 147	The Agency notes that when an anticipated treatment effect is large, eternal control designs are appropriate. This definition of 'large' is ambiguous.	BIO recommends that the Agency provide additional guidance and/or examples on 'large' effect. BIO recommends the Agency clarify if this is mainly driven by statistical significance level, numerical difference, relative improvement, or combination of all three.
Lines 147-148	The draft guidance states, "...to provide convincing results when the effect size on a well-characterized outcome of interest is anticipated to be large." The Agency should consider adding an explanation to this sentence (see proposed revision). Such vague terms may have different meanings to different readers.	BIO recommends the following revision: "... to provide convincing results when the effect size on a well-characterized outcome of interest is anticipated to be large **since the impact of bias is less likely to impact the conclusions reached by the study."** BIO also recommends the Agency consider providing descriptions of "well characterized" and "large" need to be included as part of this definition
2. Characteristics of Study Populations		
Line 156	Depending on the therapeutic area, socioeconomic status was not commonly collected as baseline characteristics in oncology trials. Therefore, comparing the similarities of socioeconomic status between external control arm and treatment arm would be difficult.	BIO recommends the Agency provide clarity on comparing the similarities of socioeconomic status between external control arm and treatment arm.
Lines 160-162	The draft guidance states, "…(2) whether such confounding factors are captured;…" Prognostic factors are often omitted from single-arm trial data collection, which is not a problem in RCTs but	BIO recommends the following edit: "…(2) whether such confounding factors are captured **in both trial and RWD**…"

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	becomes problematic with externally controlled studies. So even when the factors are measured in RWD, achieving balance is not possible unless the single-arm trial has collected them as well.	
Line 168	Some trial eligibility criteria depend on investigator judgment (e.g., likelihood of surviving a certain period into the future), which cannot be replicated in RWD. Such criteria should be avoided in the single-arm trial if an external comparator arm is planned.	BIO recommends the following addition: **"In addition, subjective criteria that cannot be replicated in RWD (e.g., likelihood of surviving a certain period into the future) should be avoided in the eligibility criteria of single-arm trials if an external comparator arm is planned."**
Lines 171-175	The draft guidance states, "Accordingly, the protocol for an externally controlled trial should include specific plans for evaluating eligibility criteria…" It is noted that the protocol should include specific plans for evaluating eligibility criteria to determine if the criteria can be applied in a manner in the external control as that in the clinical trial. However, in this context it is unclear as to what types of plans are being referred to.	BIO recommends that the Agency consider including an illustrative example to provide further clarity on the intent for this statement.
3. Attributes of Treatment		
Lines 183-185	The draft guidance states, "Such imbalances can involve factors related to the treatment of interest…" Line of therapy is not listed here as a treatment factor but is important to capture and can be much harder to do so in real-world sources.	BIO recommends that the Agency consider listing line of therapy as a treatment factor as it is important to capture and can be much harder to do so in real-world sources.

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Line 188	The Guidance focuses mostly on data coming from real world sources but does specify that EC trial designs can contain data coming from prior clinical trials	The Agency is requested to provide additional guidance on external control data coming from clinical trials.
Lines 190-196	The draft guidance states, "Clinical trial protocols typically include a plan for collecting data on use of …" This appears to only apply to retrospective RWD. FDA may consider acknowledging that intentional data capture beyond what is collected as part of SOC in a real-world study design may be beneficial here in resolving issues experienced using retrospective data.	FDA may consider acknowledging that intentional data capture beyond what is collected as part of SOC in a real-world study design may be beneficial here in resolving issues experienced using retrospective data.
Lines 203-214	The draft guidance states, "Additional factors can influence the treatment and delivery of care…" The guidance is all encompassing but if all of the factors listed here need to be accounted for then it is challenging to identify any scenario where an external control would be perfectly suitable. Even in a randomized trial there could (and often exists) an imbalance in factors, and it is hard to understand whether they are related to the drug effect or not. Many of the factors listed here appear to be upstream of the care received. This seems to be a laundry list; it would be helpful if the Agency could specify the potential impact on design. Based on the challenges outlined in this section, there are no examples or further guidance on how to bridge	BIO recommends that the guidance acknowledge that while these factors are important to account for and be discussed, the sponsor should prioritize (and support) which ones are the most critical factors that may impact the analysis. BIO also recommends that the Agency consider specifying the potential impact on design.

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	the gaps but rather the guidance just states "such factors should be identified and accounted for adequately; otherwise, a randomized controlled trial should be considered". This section lists patient-, provider-, and health-system level factors (e.g., health-seeking behaviors, access to and availability of specialty care) that are not relevant or measurable in the trial participant population and indicates that such factors should be "identified and accounted for". What does it mean to account for these factors (beyond describing the potential impact on treatment selection)? Because these factors are not relevant/measurable in the trial participant population, we cannot measure and statistically adjust for imbalances between groups.	
4. Designation of Index Date (Time Zero)		
Section 5		BIO recommends that the Agency consider including guidance on the collection of testing data (e.g., biomarker testing)
Pages 7-8, 218-227	The challenge in setting an index date when there are multiple I/E criteria that need to be met is not discussed in the guidance In a typical RCT, all the I/E criteria are assessed and confirmed at the screening visit all at once (mostly), but in RWD, I/E criteria assessments may not be available all at the same time, and setting an index date when all criteria are met is not obvious.	BIO recommends that the Agency provide more clarification on how to set the index date when there are multiple I/E criteria.

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	Difficulty in specifying the index date seems to be more specific to RWD, and not as relevant for external controls coming from clinical trials. The Agency should consider clarifying this in the leading sentence (the rest of the section seems to reiterate the emphasis on RWD)	
Line 226	The draft guidance states, "If there are temporal differences in this date relative to treatment initiation…"	BIO recommends that in addition to "treatment initiation", the Agency should consider adding duration/length of follow-up by treatment arm.
Lines 229-242	This paragraph focused on immortal time bias. It may be helpful to start with a more general statement regarding time-related biases and then narrow down to immortal time bias. For example, identifying an index date in an RWD source requires careful assessment of time-related biases. One specific time-related bias is immortal time bias. Citation; Suissa S, Dell'Aniello S. Time-relatedbiases in pharmacoepidemiology.Pharmacoepidemiol Drug Saf.2020;29:1101–1110.https://doi.org/10.1002/pds.50831110SUISSAANDDELL'ANIELLO	BIO recommends that the Agency consider starting with a more general statement regarding time-related biases and then narrow down to immortal time bias.
Section 5	When a disease is well-understood and the outcomes will not improve without treatment, it is not clear whether it is appropriate to compare the treatment effect of a test treatment to a fixed value of zero, or other relevant values or statistics.	BIO recommends the Agency provide further guidance and/or discussions on whether it is appropriate to compare the treatment effect of a test treatment to a fixed value of zero, or other relevant values or statistics. For example, if an exact value or distribution for untreated patient decline is difficult to estimate via a prospective plan, but that available data suggest

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		that patients do not improve in the absence of treatment it is unclear how to best address this.
Section 4 lines 246-248	Anchoring an index date at the occurrence of an eligibility diagnosis rather than the start of exposure may increase comparability of the clinical trial to the external control (untreated) and eliminate immortal time. However, it may decrease ability to interpret the results when events that occur prior to initiation of therapy are attributed to the treatment when there may be no causal association. While we agree with the concern over immortal time, we disagree with the proposed solution as other strategies may be more appropriate.	BIO recommends that the Agency consider other strategies that may be more appropriate to address immortal time. For a comparison of active treatment to untreated patients, several methods exist to mitigate immortal time that are less drastic than anchoring the analysis away from time of initiation of treatment. Those include using risk-set matching (selecting controls comparable to initiators at the time of initiation relative to eligibility). For example: Thomas, LE, Yang, S, Wojdyla, D, Schaubel, DE. Matching with time-dependent treatments: A review and look forward. Statistics in Medicine. 2020; 39: 2350– 2370. https://doi.org/10.1002/sim.8533) or nested design strategy with weighting: Hernán MA, Alonso A, Logan R, Grodstein F, Michels KB, Willett WC, Manson JE, Robins JM. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008 Nov;19(6):766-79. doi: 10.1097/EDE.0b013e3181875e61. PMID: 18854702; PMCID: PMC3731075.
Lines 250-254	In the situation with absence of event trigger, we can always obtain the index date for the group of test treatment as the day of initializing treatment. One common approach in the real-world setting is to obtain	BIO recommends that the Agency recognize the common approach of setting-up the index date of the external control in RWD according to the date of test treatment initiation.

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	the index date for the external control by matching the index date of the test treatment group, patient-by-patient. This is worthy of being recognized as an example in this paragraph or this section. Target trial emulation approach can help specify time zero and avoid immortal time bias etc. The Agency should clarify if this approach is encouraged to be considered in the study design.	
Page 8, Line 255	It would be helpful for the Agency to discuss the scenario when longitudinal data are available on patients in the real world setting who are followed and remained eligible across multiple lines of therapy, and how to select the line of therapy for comparison with trial data. This is common in r/r disease that patients in the retrospective RWD could meet the study eligibility criteria at baseline of multiple lines of therapy.	BIO recommends that the Agency discuss the scenario when longitudinal data are available on patients in the real-world setting who are followed and remained eligible across multiple lines of therapy, and how to select the line of therapy for comparison with trial data. In the case of a single arm trial in late-line therapy with RW external controls, several approaches for defining start of follow-up for the external controls could be evaluated with respect to bias for the treatment effect; these approaches include selecting the last eligible LoT; using information on all eligible LoT; selecting a line at random from a patient's eligible LoT or selecting a line by algorithm that minimizes the bias.
5. Assessment of Outcomes		
Section 5	**Outcome selection**: In RWD, outcomes are more likely to be recorded in clinical care when they are discrete and objective, and/or when requiring immediate medical attention, as noted in Section III. A. 5. Assessment of Outcomes. However, these types of outcomes may not be the typical measure of effect	BIO recommends the Agency comment on prioritization of these types of outcomes, especially when selecting primary vs. secondary endpoints when a RWD source is planned to be used for the external controls. The clear identification of an endpoint in RWD, including source verification and outcome validation, has a monumental impact on the results of the

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	when considering the condition of interest and investigational treatment in a clinical trial (e.g., worsening symptoms, a "soft" outcome, as opposed to hospitalization, a "hard" outcome).	study. However, it simply might not be feasible when using RWD, and the likelihood of outcome misclassification may be increased or even unknown. Therefore, there may need to be a tradeoff between selection of a disease-relevant and treatment-attributable outcome that is more subjectively measured and a slightly less relevant but objectively and definitively measured outcome. We would ask that the Agency comment on if the latter could be considered a primary endpoint, and the former a secondary endpoint, in such a scenario where it is simply not possible to have the best of both worlds.
Page 8, Line 256	The Agency should consider recommendations regarding objective biomarker endpoints (surrogate biomarker or candidate surrogate biomarkers). This will be more and more relevant and can reduce bias compared to other endpoints.	BIO recommends that the Agency add language about the potential role of such objective markers.
Section 5: 258-261	The draft guidance states, "The lack of blinding to treatments in externally controlled trials can pose challenges when considering certain outcomes,…"	Whilst definitely true that "the lack of blinding to treatments in externally controlled trials can pose challenges when considering certain outcomes," the Agency seems to suggest that this bias may only be taking place in the control arm and suggest that it was possible to blind the assessment of outcomes in those patients. In fact, when the entire treatment arm is treated (i.e. a single arm trial), is this not also the case for the treated arm? Even though these treated patient assessments are following a protocol defined schedule with strict rules about how to measure the outcome(s) all of these

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		assessments are being taken in a group of patients in which it is known that they are treated. BIO recommends the Agency provide additional clarity.
Lines 261-263	The draft guidance states "...whenever possible and for suitable endpoints, the outcome should be assessed blinded to treatment status. In some cases, this activity may require re-adjudication of the externally controlled data, such as by blinded independent central review".	BIO recommends that the Agency clarify that those outcomes captured in RWD (e.g., mortality, real-world progression, real-world response) should be sent to same BICR vendor as clinical trial patients (when possible), and not made available to sponsor until adjudication.
Lines 269-277	The draft guidance states, "Well-defined, reliable, and clinically meaningful outcomes that are typically used in randomized trials may be particularly difficult to ascertain…" This seems to be focused on the challenges of not having intentional data capture, in particular with real world data sources that may be considered for an external control arm. We suggest moving footnote 27 into the main body and expanding on registries and collecting data at predetermined intervals to help mitigate the stated issues. FDA may also consider acknowledging that intentional data capture may be beneficial in improving 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).	BIO suggests moving footnote 27 into the main body and expanding on registries and collecting data at predetermined intervals to help mitigate the stated issues. FDA may also consider acknowledging that intentional data capture may be beneficial in improving 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).

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Lines 271-272	The draft guidance states, "For example, radiologic endpoints in controlled oncology trials…" Response rate and PFS limitations related to assessment frequency are described together as one. However, RR is impacted less than PFS by the assessment frequency.	BIO suggests the Agency consider differentiating the impact of RECIST and assessment frequency on RR and PFS. It would also be helpful to describe the Agency's equivalent thinking for OS.
Lines 271-277	In routine clinical care, radiologic assessment frequency for oncology treatments is variable, and formal tumor measurement may not routinely be performed or documented, making a valid assessment of PFS or objective response rate using external control data challenging.	BIO recommends that the Agency clarify which endpoints are recommended for the collection of RWD in oncology. BIO also recommends that the Agency clarify when surrogate endpoints are appropriate. If a valid assessment cannot be collected in RWD, are surrogate endpoints appropriate? For example, Time to Next Treatment for Progression Free Survival.
Lines 280-283	The draft guidance states, "As another example, a randomized trial may include specific testing to detect or confirm…" In addition, measurement of certain outcomes may be done differently in a clinical trial and routine clinical care/RWD. For example, different scoring system, coding system (ICD 9 versus ICD 10) or cut-offs for markers may be used for defining certain outcomes in an RCT and routine clinical care. This will introduce measurement bias.	BIO recommends that the Agency further clarify that measurement of certain outcomes may be done differently in a clinical trial and routine clinical care/RWD.
Lines 286-288	The draft guidance states, "…when events are objective and/or require immediate medical attention…"	BIO recommends the following edit:

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	Outcomes are more likely to be recorded when they are part of routine clinical care for the patient population.	"…when events are objective, **part of routine clinical care for the patient population**, and/or require immediate medical attention…"
Page 9, 290-292	The draft guidance states, "…sponsors should also evaluate the consistency of timing of outcome assessments…" is missing the handling of recall period for measurement of outcomes. Different recall periods for the outcome of interest (e.g. if derived from PRO) can result in substantial confounding of results	BIO recommends that the Agency include a statement on recall period for evaluating endpoints.
Lines 296-298	The draft guidance states, "…at what intervals the outcome of interest should be assessed in the analysis of data from an externally controlled trial." Intervals for data collection in the single-arm trial can be informed by RWD; a trial may insert additional measures, but using a baseline of usual care will improve comparability.	BIO recommends the following edit: "…at what intervals the outcome of interest should be assessed in **the single-arm trial and in** the analysis of data from an externally controlled trial."
Lines 298-301	The draft guidance states, "Based on such determinations, sponsors can then evaluate whether the availability and timing of the outcome assessments are sufficient and comparable across both arms of the externally controlled trial for the research hypothesis being tested." Making the arms technically comparable may not be necessary. For example, time to event assessments may follow different schedules for the study and	BIO recommends the following revision: "Based on such determinations, sponsors can then evaluate whether the availability and timing of the outcome assessments are sufficient and comparable *or* ***adequately adjusted for analysis.***" ~~**across both arms of the externally controlled trial for the research hypothesis being tested."**~~

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	external controls, but in the right conditions, interval censoring methods will account for the uncertainty appropriately. Guidance speaks to assessing comparability in outcomes between clinical trial and RWD. Are sponsors encouraged to perform outcome validation studies for clinical endpoints to demonstrate concordance between outcomes captured in RWD versus a clinical trial (e.g., comparing ORR or PFS based on RECIST methodology versus real-world response and real-world progression in a subset of patients)? It would be helpful if the Agency could provide a table on considerations for assessing outcomes, that is similar to the table -Summary of Considerations for Assessing Comparability of Data.	
Page 13, Line 314	The guidance on 'intercurrent events' addresses the impact on potentially impairing the interpretability of treatment effect. However, the guidance does not address the impact on safety regarding confounding factors and how this could be mitigated to give a clearer picture of the related safety events. For example, if different sub-groups of patients are taking different medications for comorbidities, how could this be further addressed to utilize the safety information generated from the external study?	BIO recommends adding examples of challenges related to interpretation of safety assessment and potential analyses that could be considered.

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	Safety from clinical data derived from external trials will need to be appropriately evaluated or compared so that it could be used as supportive data in the appropriate context. If there is a significant deviation in patient medical history or concomitant medications, this could impact the accuracy of the safety assessment, so guidance on this topic would be helpful for the sponsor when considering the design of safety analyses for externally controlled studies.	
Lines 314-316	The draft guidance states, "Further challenges may arise from differential capture of intercurrent events that may preclude the measurement of or impair the interpretability of the treatment effect on the outcome of interest." Challenges in capturing intercurrent events are important points, but this section (5. Assessment of Outcomes) may not be the best place to describe as intercurrent events are not always outcomes.	BIO recommends the Agency consider moving this statement to A. Design Considerations 1. Overview.
B. DATA CONSIDERATIONS FOR THE EXTERNAL CONTROL ARM		
Entire Section	There is no discussion of special considerations when several clinical trials are available to build the external control arm.	BIO recommends that the Agency consider discussing special considerations when several clinical trial are available to build the external control arm.
1. Data from Clinical Trials		
Lines 339-341	Original text: "A particular concern for bias would be the selection of an external control arm from a completed trial whose outcomes are already known. This would be especially	BIO recommends that the Agency clarify "prior experience" to make it clear what the "prior experience" refers to in this context. Since the results of the external control arm are from the completed trial, does the statement infer inconsistency

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	problematic if the results of the external control arm are inconsistent with prior experience." In discussing "prior experience" in this context, we think that the Agency's concern is intentional selection of an external control that biases the result when those external control data differ from prior experience. If this understanding is correct, we suggest that the Agency be more direct in stating its concern. It is understandable that ideally, an external control arm should be identified prior to knowing the outcome of the associated external trials. But these two sentences about bias may not be particularly helpful in certain situations because (1) published ("known") clinical trial results are a natural source for seeking external controls, and (2) in order for "prior experience" to be credible, it is likely to have been published and therefore "known". Whilst this may be true, how can they practically expect this to be applied in situations when you want the external arm to be treated with a different medication i.e. (Current SOC) which is a medication the sponsor does not manufacture. No company will be able to obtain patient level data (the focus of this guidance) from another company's trial until that trial is completed and reported out). This section 5.1 needs	between the known completed trial and the "prior experience?" It would be most helpful to specify that the selection of the control arm should not be based on knowledge of the outcomes. Rather it should be based on similarity of the population and other comparability considerations mentioned in subsequent sections. The recommendation is to reframe these statements. If the disease progression is well understood and predictable and the external control data are consistent with prior natural history knowledge, it can be acceptable to use external control arm. It is proposed to revise language to "**An external control arm from a prior trial is acceptable if the results are consistent with prior natural history experience for the disease**."

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	some more context setting about circumstances when it may/may not be appropriate to use other trial data.	
Line 333	The draft guidance states, "Using data from another clinical trial …." Baseline-controlled study could also be considered that the data were collected prior to the initiation of the experimental treatment. i.e., it does not have to be "another" clinical trial.	BIO recommends that the Agency clarify that it does not have to be "another" clinical trial.
Lines 335-338	The draft guidance states, " Such use would only be appropriate, however, when comparability exists…" It would be helpful if the Agency provided more granularity for what "comparability exists" means. Are there situations where sufficient comparability for all the listed domains is not required for the utility of an external control arm to be "appropriate"?	BIO recommends that the Agency provide more granularity for what "comparability exists" means. BIO recommends that the Agency clarify if there are situations where sufficient comparability for all the listed domains is not required for the utility of an external control arm to be "appropriate".
Line 336	It's unlikely complete comparability can be assured when using external controls, however a certain degree of comparability, and especially focused on criteria that is known or suspected to affect disease or response to treatment, may be adequate. Comparability is described to be a key consideration, but the guidance does not address comparability studies (or validation studies) to evaluate and establish comparability of key study elements	BIO recommends the following edit: "Such use would only be appropriate, however, when ***a reasonable degree of*** comparability exists between the two trial arms…"
Line 338	The draft guidance states, "A particular concern for bias would be the selection of an external control arm from a completed trial whose outcomes are already known."	BIO recommends that the Agency further discuss consideration of the adaptation of eligibility criteria and exposure data

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	Isn't this always the case when using data from other [historical] clinical trials? These trials are completed and thus available for use as historical control data. The guidance focuses on identifying suitable CT or RW data that are comparable to a study arm in CT. How about adaptation of eligibility criteria and exposure data collection in trials to be more comparable to an externally controlled RWD arm? Does this restrict external control data only from ongoing studies?	collection in trials to be more comparable to an externally controlled RWD arm.
Lines 340-341	It is unclear whether "prior experience" is from data that can be incorporated into external control or from experts' opinion. During discussion of an external control arm for a specific trial, will such "prior experience" be specified to avoid any confusion or uncertainties in trial design and external control data selection?	BIO recommends that the Agency clarifies the meeting of "prior experience".
2. Data from RWD Sources		
Entire Section		BIO recommends the Agency clarify if the external data is already submitted to FDA, can that be referenced instead of resubmitting, especially if the data is "owned" by another entity from the MAH for the current submission. BIO also recommends that the Agency clarify the requirement for ECA data submission comparing to clinical trial data package. Specifically, if the ECA is created using RWD, does it

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		need to be converted to clinical trial format (STDM and ADAM-like data set).
Table between Lines 374 to 376	The list of considerations in this table do not fully map and are not always consistent with the subsections in the document. Clarifying the table and harmonizing with the rest of the document will help sponsors present information that is relevant to the FDA in their evaluation of fitness for purpose and impact of potential sources of bias on findings	BIO recommends that the Agency consider harmonizing the list of considerations throughout the document so that Table 1 serves as a summary. For instance, it is unclear whether sponsor should address all those considerations in the table in their fitness for purpose assessments or whether to focus on those that may induce bias in the comparison (away from the null, more favorable to the test drug) from the null). Other sections in the document (e.g., overview, lines 62-63, lines 122-133) seem to particularly highlight prognostic factors among confounders and misclassification (e.g., immortal time) that would lead to bias directionally in favor of the test drug.
Page 12, 374-375	The Agency should clarify if the intercurrent events could not be assessed reliably, how would that translate in terms of its impact on the estimand definition? Are there statistical methods to address this? For e.g., treatment discontinuations, use of rescue medications and the corresponding estimand definitions are per protocol in RCTs. But, in RWD, the reasons for discontinuation or whether a rescue medication was used may not be available (or done for a different reason).	BIO recommends that the Agency provide more detail on the potential difference in the definition and assessment of intercurrent events between the RCT arm and the external control arm and its impact on the estimand definition.
Lines 359-360	If missing data is a concern, can data completeness be a criterion in selecting RWD for external control?	BIO recommends that the Agency discuss data completeness as a criterion in selecting RWD for external control.
3. Considerations for Assessing Comparability of Data Across Trial Arms		
C. ANALYSIS CONSIDERATIONS		

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1. General Considerations		
Section	**Scope and role of feasibility assessment**: There are a number of considerations that cannot be assessed or addressed in a prespecified protocol and statistical analysis plan until feasibility assessments are conducted, especially when a real-world data (RWD) source is to be used for the external controls, as mentioned in the general considerations in Section III C. 1. General Considerations.	BIO suggests additional details of such a feasibility assessment be incorporated into this guidance document. It is clear a feasibility assessment is a critical part of taking into account all of the considerations delineated in this document. Recommendations on what to prioritize (e.g., ensuring similar study populations) in such an assessment, as well as to what extent data can be examined in a feasibility analysis to maintain blinded outcomes, could also benefit this guidance. The timeline of this type of assessment is also important to account for, given the study must be designed after taking into account the feasibility findings. We would recommend emphasizing the crucial aspect of a feasibility assessment to address study design concerns, conducting this assessment as early as possible with a limited data cut (e.g., just baseline characteristics or an earlier time period) to maintain a blinded approach, and discussing findings and conclusions with the Agency prior to the study protocol development.
Line 387	The draft guidance states, "…calculations of statistical power and sample size…" If using retrospective data to create an External Control Arm, a common approach is to include all eligible patients identified from the database and then use e.g., matching, or weighting criteria to adjust for baseline confounders. In this case we do not know a priori which of those patients will end up being included or how much weight will be given to each patient, so it is	BIO recommends that the Agency clarify expectations for sample size/power calculation in these situations. Specifically, it would be helpful if the Agency could clarify that an externally controlled trial may be designed with the goal of estimation rather than formal hypothesis testing. If the focus is on estimation, the sample size should be set to achieve a certain precision for estimating the treatment effect of interest. Relevant operating characteristics would then also need to be aligned with the goal of estimation, such as bias,

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	difficult to determine the effective sample size of the external control arm in advance. Please clarify expectations for sample size/power calculations in such situations. The current text focuses on the use of the external controls for formal hypothesis testing. However, this may not be the goal for all externally controlled trials. Some externally controlled trials may be designed with the goal of estimation rather than formal hypothesis testing, particularly in the context of exploratory trials or studies meant to provide context to single arm trials. The design of the study should be aligned with its objective. The draft guidance states power calculations and sample size should be calculated prior to the study but also that decisions regarding study design and analysis should be blinded. It seems that the external control data may be used to inform power and sample size of a new trial when the external data are available at the time of planning a new study. The external data, in this scenario, are not random and therefore the external control is, in essence, used as a threshold-crossing approach for the new study objectives.	confidence interval width and standard error of the treatment effect estimate.
Line 388	It is unclear whether or not the detailed main statistical analysis plan should be combined in the same document as the study protocol for submission or if the	BIO recommends that the Agency provide clarity on whether the detailed main statistical analysis plan should be combined in the same document as the study protocol for submission or

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	statistical analysis plan and study protocol should be submitted as two separate documents.	if the statistical analysis plan and study protocol should be submitted as two separate documents.
Lines 388-389	The draft guidance states, "The statistical analysis plan should be submitted along with the protocol to the relevant review division before initiation of enrollment in the clinical trial for the experimental treatment."	Similar to the Agency's accepted approaches for conventional clinical trial SAPs - although it is ideal for the final SAP to be submitted before clinical trial enrollment, BIO recommends that the guidance acknowledge that it may be acceptable in some situations for the final external control SAP to be submitted to FDA after the start of the clinical trial enrollment but before the planned analysis cutoff (and before any outcome data could be viewed). Consideration may also be given in cases where there may be a separate clinical trial SAP and external control comparison SAP.
Lines 388-390	This guidance requires that the Protocol/SAP of externally controlled trial be submitted to the relevant committee for the review BEFORE initiation of enrollment in the clinical trial for the experimental treatment. It, however, is unrealistic because: 1. The SAP of the clinical trial normally would not be finalized until it gets close to the database lock (e.g., 2 weeks prior to database lock). Therefore, requesting the SAP of the externally controlled trial to be ready for the review prior to the clinical trial enrollment may be impractical. 2. If the clinical trial of the experimental treatment does not meet the expectation as it aims for, then there is no need to run an externally controlled trial. i.e., the required work for the externally controlled trial may be wasted.	BIO recommends that the Agency clarify whether this is referring to a final SAP or a draft SAP.

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Lines 390-393	Original text: "In addition, decisions regarding the study design and statistical analysis plan for an externally controlled trial should be blinded to any observed external control data (e.g., from an existing RWD source), with the exception of planned feasibility analyses, such as evaluating the availability of key variables or missing data." BIO recommends clarification that the exception may include baseline variables prior to the index date in the external control arm to allow the monitoring of the number of eligible patients and balance of the treatment arms and external control. It is stated that the decision on the study should be blinded to external control, except for feasibility assessment. A fairly comprehensive feasibility assessment may be required, and it may be difficult to maintain blinding when undertaking this. To finalize a statistical analysis plan, review of observed external control data may be necessary, but accessing outcome data should be avoided. It is unclear what FDA expectations are for acceptable vs unacceptable feasibility analyses. For instance, to what extent are researchers permitted to work with outcome data when assessing feasibility?	BIO agrees with pre-specification of the design and analysis plan prior to any unblinded access and analysis of treatment outcome data. However, it is important to monitor the level of propensity matching and baseline covariate balance during trial conduct, especially for studies with concurrent external control. Thus, BIO recommends that the Agency clarify that "baseline data" may be accessed during the trial conduct prior to "unblinding" for comparative analysis of outcome data. BIO recommends that the Agency reference existing guidance that provides direction on how to maintain appropriate blinding while completing feasibility; otherwise, some additional advice on how to maintain blinding would be helpful (e.g., the feasibility could be completed by another group that is not otherwise involved in the study design). BIO recommends the following revision: "In addition, decisions regarding the study design and statistical analysis plan for an externally controlled trial should be blinded to any observed ***outcome data from external controls.***" BIO recommends that the Agency clarify that the approach that will be used to evaluate feasibility should be documented in an analysis plan which should be agreed between the sponsor and FDA.

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	Planned feasibility analyses could address a broad set of considerations, including assessments that work with outcome data, such as power calculations. More concrete guidance would be helpful on appropriate/transparent ways to conduct feasibility analyses used to inform protocol/SAP so as not to create appearance of "data-peeking" or "cherry-picking" results in any way. Should feasibility analyses be included in audit trail? Many statistical aspects may be modified during the course of the trial as in randomized controlled trials. Such modifications include excluding variables in analysis models due to poor data quality and excluding one data source due to data collection difference. These issues often cannot be identified without thorough examination of the data. More guidance is needed.	
Line 396-397	The draft guidance states statistical analyses changes during the study should be "discussed with the relevant FDA review division." The Agency should clarify if there is a specific type of meeting that should be requested for such discussion. It is also unclear whether the sponsor should pause the trial for such discussion.	BIO recommends that the Agency specify what type of meeting should be requested for further discussion and what course of action are required for a statistical analysis plan change.
Page 16, Line 399	Methodology: It is acknowledged that there is no single fit for purpose solution. Nevertheless, it would be helpful to get some suggestions from the FDA on	BIO recommends that the Agency consider adding a list of methods with their pros and cons.

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	preferred approaches that may be employed in different situations.	
Lines 402-403	Line 402-403 states "Sponsors should provide a justification for the analytic methods selected as well as a description of the strengths and limitations of the methods used to assess the effect of treatment."	BIO recommends that the Agency clarify if the justification and description of the strengths and limitations of the methods should be provided in the statistical analysis plan.
Line 415	These measures are a nice way of having a general description of how similar the external to internal arms are, but BIO recommends the focus be on whether the covariates in the similarity measure influence any potential confounding of a treatment effect.	BIO recommends that the focus is on whether the covariates in the similarity measure influence any potential confounding of a treatment effect.
Lines 423-426	The draft guidance states, "Consideration should also be given, based on available scientific data, to the anticipated effect size for analyses of the primary endpoint. Especially when the anticipated effect size is modest, an externally controlled trial may not be an appropriate study design because of concerns for bias affecting the results." This point is very important, but the section (C. Analysis Considerations, 1. General Considerations) may not be the right place for it. This is rather related to whether externally controlled trials can be selected or not from a design perspective. While treatment effect may be modest in certain situations, there may be other benefits of a treatment such as significantly improved safety profile, etc.	BIO recommends that the Agency consider moving this statement to A. Design Considerations 1. Overview. BIO also recommends that the Agency provide more concrete guidance on the determination of modest for the effect size. BIO recommends that the Agency considering clarifying if such other benefits, such as significantly improved safety profile, could influence the benefit-risk balance to consider an external control approach.

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Line 426	The draft guidance states, "…because of concerns for bias affecting the results." Bias may affect the magnitude, and analytic methods to control or assess bias can affect the precision of effect estimates.	BIO recommends the following edit: "…because of concerns for bias affecting the **magnitude and precision of effect estimates** ~~results~~."
2. Missing Data		
Line 438-440	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."	BIO recommends that the Agency provide more guidance for the situation where missing data is unverifiable and difficult to justify.
3. Misclassification of Available Data		
Entire Section	Line 458, 3. Misclassification of Available Data: Misclassification seems mainly due to different practices in the data collection or assessment and thus should be included in the section of 5. Assessment of Outcomes (Line 256)	BIO recommends the Agency clarify the difference or recognize the connection between the sections on Line 458 and Line 256. If the misclassification of data comes from data collection or assessment, the section of Misclassification of Available Data may be combined with Assessment of Outcomes.
Lines 465-467	Original text: "[…] inaccurate reporting by patients about their alcohol intake because of stigma or other factors, differences in the approach used to classify alcohol use within or across various sources of data can lead to misclassification."	BIO recommends the following revision: "[…] inaccurate reporting by patients about their alcohol intake because of stigma or other factors, differences in the approach used to classify alcohol use within or across various sources of data can lead to misclassification **in all types of trials, including externally controlled trials**."

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	We believe that these types of biases impact all studies, not just EHR or RWD-based studies as positive responder/self-report bias.	
Line 472	The draft guidance states, "If misclassification is extensive…" Misclassification would only have an impact when it occurs in variable types listed.	BIO recommends the following edit: "If misclassification is extensive **for variables defining treatments, outcomes, or confounding factors** …"
4. Additional Analyses		
Entire Section	This section does not have specific guidance on externally controlled trials. More guidance is needed on what type of additional analyses should be considered for externally controlled trials.	BIO recommends that the Agency provide additional guidance on what type of additional analyses should be considered for externally controlled trials.
IV. CONSIDERATIONS TO SUPPORT REGULATORY REVIEW		
A. Communications with FDA		
Page 16, line 496-503	The draft guidance states, "Sponsors should consult with the relevant FDA review division early …" The guidance says early, but then states, "sponsors should provide a detailed description of the… (3) planned statistical analyses". It is unclear if FDA expects sponsors to come to them with a protocol/SAP or if this is a multi-step engagement. It would be helpful to clarify when and how to engage FDA and the Agency expectations for the protocol and SAP to have an effective conversation with FDA.	BIO recommends that the Agency clarify whether the protocol and SAP are part of this early interaction or whether there are two steps of 1) early design concept and 2) protocol/SAP review.
Lines 498-503	Original text:	BIO recommends the following proposed changes:

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	"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. As part of these discussions, sponsors should provide a detailed description of the (1) reasons why the proposed study design is appropriate, (2) proposed data sources for the external control arm and an explanation of why they are fit for use, (3) planned statistical analyses, and (4) plans to address FDA's expectations for the submission of data." BIO appreciates the Agency's description of the information necessary and requests additional details regarding a fit-for-purpose assessment of the data, study design, and analysis plans to meet the research question. Externally controlled trial is an alternative to single-arm trial alone and to RCT. Sponsors would benefit from knowing if the protocol is also recommended in addition to statistical analysis plan prior to discussions with the Agency.	"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 single-arm trial alone or instead of a** randomized controlled trial. As part of these discussions, sponsors should provide a detailed description of **(1) the research question (2) proposed data sources and results of feasibility assessments to inform fit-for-purpose/use (3)**~~(1) reasons why~~ the proposed study design ~~is appropriate, (2) proposed data sources for the external control arm and an explanation of why they are fit for use,~~ (**4**~~3~~) planned statistical analyses, **(5) sponsor determination that the data, study design, and** analyses **are fit-for-purpose/use** and (**6**~~4~~) plans to address FDA's expectations for the submission of data." BIO recommends the Agency clarify if the study protocol for external control study is required to facilitate the communication with FDA.
B. Access to Data and Documents		
Entire Section	For external data, clarify if submission of this data should follow other guidance or if additional guidance may be developed for this not otherwise included in	BIO recommends that the Agency clarify if submission of this data should follow other guidance or if additional guidance may be developed for this not otherwise included in other

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	other guidance, e.g., in antivirals there is guidance on format/content of submission datasets for clinical trials. Some data domains may be much different for RWD (e.g., viral resistance), so it would be helpful to understand if some flexibility for submitting this data exists, especially when data is real world and and/or historical clinical trial data.	guidance, e.g., in antivirals there is guidance on format/content of submission datasets for clinical trials.
Page 16, line 507-513	The draft guidance states, "Sponsors must include in their marketing applications relevant patient-level data." "Sponsors should also ensure that FDA has access to source documents and source data for the external control arm as part of an FDA inspection or upon request." For some healthcare databases, the data may be de-identified patient-level data. Sponsors may not have direct access to patient level or source data from third parties, including clinical trials. More guidance would be helpful on how data from RWD control arm patients should be delivered. For example, should it be delivered in the format as delivered by the data owners (e.g., vendors) with appropriate analytic code to create derived variables, align with clinical trial data, apply weights, etc.? Or	BIO recommends that FDA clarify/affirm that de-identified patient-level data are allowed and specify a range of mechanisms to provide access to data to meet FDA's requirements.

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	should data be delivered after such modifications are made?	
Lines 512-513	In case access to source documents is prohibited, sponsors should ensure the FDA has access to the detailed process of converting source documents to data. Real world data sources used for generating the ECA may be derived from curated data from medical charts and access to the source data may be very limited due to privacy regulations/requirements.	BIO recommends the following edit after line 513: **"In case access to source documents is prohibited, sponsors should ensure FDA has access to the detailed process of converting source documents to data."**
V. GLOSSARY		