March 8, 2022

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

Re: Docket No. FDA–2021-D-1214: Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

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(BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance on **Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products**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.

BIO appreciates the opportunity to comment on this draft guidance and the previous draft guidance on *Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products, Data Standards for Drug and Biological Product Submissions Containing Real-World Data and Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products.* Across this series of draft guidance, BIO emphasizes the need for the Agency to:

- **Incorporate an appropriate degree of regulatory flexibility** into the draft guidance that is tailored to the specific context for the RWD, and how it can support a regulatory decision as part of a totality of evidence
- **Identify streamlined and efficient FDA-sponsor communication methods to facilitate rapid evidence generation** by providing more clarity on the amount and types of information required to have a robust and productive discussion with the Agency
- **Identify best practices for data curation, processing and governance** by working with stakeholders to better understand and address the practical realities of improving RWD quality and meeting the Agency's expectations

Given the breadth and depth of this series of draft guidance and the forthcoming draft guidance on *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products and Using Clinical Practice Data in Randomized Controlled Trials (RCT) for Regulatory Decision-Making for Drug and Biological Products,* BIO recommends that the Agency consider engaging with stakeholders through a series of workshops and/or meetings to better address challenges and identify opportunities to improve the use of RWD/E in regulatory-decision making.

BIO looks forward to working with the Agency to improve the use of RWD/E in regulatory decision making and recommends the following key considerations to improve this draft guidance:

Scope of Guidance

As FDA noted in the draft guidance: "FDA recognizes the potential utility of using RWD in interventional studies; for example, to identify potential participants for a randomized controlled trial, to ascertain endpoints or outcomes (e.g., occurrence of stroke or other discrete events, hospitalization, survival) in a randomized controlled trial, or to serve as a comparator arm in an externally controlled trial, including historically controlled trials. However, the guidance only provides "Regulatory Considerations for Non-Interventional (Observational) Studies". We suggest FDA provide information on Regulatory Considerations for using RWD in interventional studies as well, since RWD are commonly used as a comparator arm to a single arm clinical trial.

We also note the draft guidance does not address the case where sponsors are required to work with a third party to access RWD which may be in a jurisdiction outside of the US. In these cases, the third party may not own or host the data and may only receive the results of analyses. As such, the third party may not be permitted to share data copies directly. We recommend the guidance be modified to address this very common use case.

Opportunities for RWD/E Collaboration

The FDA is to be commended for making public how it is starting to organize the review of "various clinical study designs that utilize RWD submitted to the FDA in support of regulatory decision-making regarding the effectiveness and safety of a drug...". The FDA has attempted to provide direction for non-interventional study designs (observational cohort studies and case-controlled studies) that use RWD. Much of the narrative in this guidance attempts to align considerations for the use of RWD with FDA regulations under Title 21 CFR Part 312 B, Part 314, and to some degree Part 601.

While these existing regulations provide a foundation on which to build the use of RWD, they will require collaborative efforts with researchers, data vendors, data scientists, bioinformaticists, and policy makers (ONC CMS) to accommodate the impact of the growing number of digital data sources used as RWD in non-interventional (and even interventional) studies. BIO recommends that the Agency consider this key opportunity to work with the broad range of stakeholders who are part of the broader RWD

generation ecosystem, in order to provide clear guidance on how researchers can both collect and leverage RWD that is fit-for-purpose for regulatory decisions.

In addition, given that many for-profit data vendors provide de-identified licensed data to sponsors, BIO recommends that the Agency engage this growing business sector to collaboratively establish best practices and expectations. BIO recommends that the Agency establish a mechanism to meet with these data vendor organizations to address broad ranging topics that are outside the scope of a specific drug development program.

The current guidance also reflects that training and education is required within the regulatory science, policy making, data science, bioinformatics, and amongst public/private observational research communities to better leverage the rich RWD sources that can be used for regulatory purposes. BIO recommends that the Agency take the opportunity to organize training so that stakeholders collaboratively and collectively learn how to best leverage the potential benefits of RWD.

FDA-Sponsor Engagement

Throughout the draft guidance, BIO agrees with FDA's recommendations for sponsors to engage with the Agency early and often when use of RWD/E is intended to support a regulatory action. However, the current communication channels and processes may not be adequate for such engagements. To encourage appropriate use of RWD/E within the regulatory decision-making framework, sponsors need timely feedback from FDA. As stated on Line 136, one available option mentioned within the draft guidance is a Type C meeting.

The final guidance could more clearly outline the appropriate mechanisms for obtaining timely and efficient Agency feedback, especially in light of the upcoming Advancing RWE Program and Type D meeting option outlined in PDUFA VII. BIO recommends that the Agency further clarify in the final guidance how and when to receive feedback from the Agency, including how FDA plans to address the need for multiple interactions, and the associated timelines.

In addition to understanding the timing and nature of expected engagement, BIO believes it would be helpful for FDA to articulate what supporting documentation is needed at each stage of engagement (e.g., study outline, draft protocol and statistical analysis plan (SAP), approved protocol and SAP, and the need for feasibility analyses) to ensure meaningful and robust interactions prior to study conduct. For example, it would be beneficial for FDA to clarify whether feasibility studies are recommended to be conducted prior to the request of a Type C meeting, or whether sponsors need to engage with FDA to align on suitable approaches prior to the conduct of these studies.

Lastly, BIO recommends that the final guidance outline that beyond the appropriate review division, RWD/E subject matter experts within FDA are required for these Agency discussions (e.g., Office of Surveillance and Epidemiology, Office of Medical Policy RWE Subcommittee, etc).

Additional RWD/E Examples Needed

Throughout the draft guidance, the requirements for non-interventional studies using RWD/E do not appear to differ depending on the regulatory decision in scope and the weight of evidence the RWD/E is providing (i.e., how it contributes to the totality of evidence). BIO recommends that the final guidance include several examples in the appendix for how different contexts of use for RWD/E studies could satisfy FDA's recommendations for different regulatory decisions.

BIO also recommends that the Agency provide examples of studies and how they may be treated as per the guidance and whether the IND regulations apply (e.g., external controls). BIO also recommends that the Agency consider providing examples that clarify adverse events and safety reporting, how to conduct and handle feasibility studies and consideration for the use of Artificial Intelligence/Machine Learning (AI/ML) in study design and patient selection.

Harmonization of RWD/E Guidance and Future RWD/E Guidance

BIO recommends that the Agency combine, streamline, or cross reference the RWD guidance documents for ease of use and to avoid confusion. BIO also recommends that the Agency update the guidance to take a risk-based or fit-for-purpose approach to regulatory considerations, considering how RWD/E contributes to the totality of evidence. Specifically, BIO requests that the Agency provide considerations for both hypothesis testing studies meant to provide the main support for regulatory approvals, and for studies that are meant to support decisions as part of the totality of evidence.

Looking across the four RWE guidance documents released in 2021, the topic of study design/analysis has not been covered (though this topic is implied in the EHR/Claims and Registry guidance as forthcoming). It was envisioned when Cures (and PDUFA VI) were drafted that this guidance would address the circumstances where FDA may rely on RWE to support label expansion, including how sponsors should approach this use case should they choose to do so. BIO looks forward to future guidance on the Agency's expectations on appropriate regulatory and clinical contexts of use, study designs, and analytical approaches while also maintaining an adequate amount of flexibility.

BIO also encourages the Agency to address foundational concepts like how a non-interventional study can be 'adequate and well controlled' and meet regulatory requirements in future guidance given that this concept has been addressed in recent approvals but absent from the draft guidance documents. Without this important guidance, the level of uncertainty about the Agency's willingness to accept RWE will continue to impede uptake. The Duke Margolis Center for Health Policy RWE Collaborative has published papers addressing best practices in observational study design and analysis, how such studies may be adequate and well-controlled, and the totality of evidence approach:

- Understanding the Need for Non-Interventional Studies Using Secondary Data to Generate Real-World Evidence for Regulatory Decision Making, and Demonstrating their Credibility (duke.edu)

- Adding Real-World Evidence to a Totality of Evidence Approach for Evaluating Marketed Product Effectiveness (duke.edu)

BIO encourages the FDA to consider developing guidance focused on considerations for the use of distributed networks as a source of RWD and the derived RWE when used to support regulatory decision-making. All four FDA guidance published to date focus mostly on RWD that can be accessed and analyzed by sponsors, implying that patient-level data should be the basis of the analyses and should be shared with the FDA. There is a growing body of RWD that is part of a distributed network (e.g. Sentinel, PCORnet) and the available data is analyzed locally and then combined by a central, independent-from-sponsor data coordinating center. The model of a distributed network is also being explored in a global setting.

Sincerely,

/s/
Camelia Thompson, Ph.D.
Senior Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

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I. INTRODUCTION		
Lines 25-28	The draft guidance state, "FDA is issuing this guidance as part of its RWE Program to satisfy…" The scope of the guidance is given as "postapproval" e.g."new indication for an already approved drug". However, a non-interventional study (NIS) could also be part of a registration trial.	BIO recommends that the Agency clarify whether the guidance could apply in pre-approval situations e.g. if the external control arm is based on a non-interventional study (NIS) using vendor data. BIO recommends that the Agency provide more clarity on what RWE this particular guidance is relevant for (i.e., is RWE used in linkages or comparisons to trial data and/or RWE that characterizes heterogeneity in patent population or assessment of class of products/different mechanism of action (MOA) in scope of this guidance?)
Lines 38-44	Safety signal detection and near real time safety monitoring do not appear to be in scope of this guidance. Further, the recommendations of the guidance would not be applicable for these activities. However, the definition of *clinical study* in footnote 6 indicates that safety signal detection and monitoring would be in scope for the guidance.	BIO recommends that the applicable safety and pharmacovigilance FDA and/or ICH guidances be explicitly referenced with their relevant sections from the guidance cited in this guidance and that a dedicated section on safety reporting be expanded in this draft guidance for clarity.
Line 32-33	The draft guidance states, "RWD are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources." The provided definition of RWD lacks clarity on which data collection (primary data vs. secondary use of data) is in scope of the guidance. The current definition suggests that only routinely collected data are in scope of the guidance which	BIO recommends adding the following sentence: "**Specifically, data collected from routine medical practice."** BIO also recommends that the Agency consider referencing the examples of RWD and RWE provided in the FDA RWE Framework, along with definition included in the website https://www.fda.gov/science-

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	would exclude use cases involving primary data collection.	research/science-and-research-special-topics/real-world-evidence
Line 43-44:	The draft guidance states, "This guidance focuses primarily on clinical study designs that are non-interventional."	BIO recommends that this sentence is moved to the beginning of the paragraph.
II. BACKGROUND		
Lines 62-64	The draft guidance states: "Clinical trials with pragmatic elements (e.g., broad eligibility criteria, recruitment of participants in usual care settings) and single-arm trials are other types of interventional study designs." With the increasing application of external control for single-arm trials, it would be helpful for the final guidance to clarify whether the study to collect external control data is considered part of the interventional study or is still considered a non-interventional study.	BIO recommends that the final guidance clarify whether the Agency views the RWD/E external control arm as part of the interventional trial for regulatory purposes (i.e., submission of the protocol to the IND is required).
Lines 62-64	The draft guidance states, "Clinical trials with pragmatic elements…" Pragmatic studies are an important element considered in regulatory decision and clarification of the definition can help the companies to align on Agency expectation	BIO recommends that the Agency clarify the definition of "pragmatic".

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Lines 66-74	The draft guidance states, "For the purposes of this guidance, a non-interventional study…" The creation of an external control arm is likely to be a common use-case of real-world data. It would therefore be helpful to clarify whether the principles outlined in Section III.B apply to this application.	BIO recommends that the Agency clarify whether creation of an external control arm would be regarded as a non-interventional study in this context (i.e. it could be seen as an observational cohort study).
Line 68-74	The draft guidance states, "Examples of non-interventional study designs include (1) ***observational cohort studies***, in which patient…" The examples given for non-interventional study designs are 'observational' cohort studies and case-control studies. Case-control studies are also observational; the use of 'observational' for cohort studies is unnecessary. It may be helpful to provide more examples or additional details regarding non-interventional study designs (e.g. cohort studies could be prospective, or retrospective; studies could involve primary data collection or use of secondary data or a hybrid approach)	BIO recommends that the Agency consider providing more examples or additional details regarding non-interventional study designs (e.g. cohort studies could be prospective, or retrospective; studies could involve primary data collection or use of secondary data or a hybrid approach) BIO recommends that following edit: "Examples of non-interventional study designs include, **but are not limited to,** (1) ***observational cohort studies***, in which patient…"
III. REGULATORY CONSIDERATIONS ADDRESSED		
A. Applicability of 21 CFR Part 312		
Lines 93-97	The draft guidance states: "Interventional studies involving drugs generally meet the definition of a clinical investigation under § 312.3 and are subject to FDA regulations under	BIO recommends that the final guidance clarify whether the Agency views the RWD/E external control arm as part of the interventional trial for regulatory purposes (i.e., submission of the protocol to the IND is required).

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	part 312 as described in § 312.2. FDA recognizes the potential utility of using RWD in interventional studies; for example, to identify potential participants for a randomized controlled trial, to ascertain endpoints or outcomes (e.g., occurrence of stroke or other discrete events, hospitalization, survival) in a randomized controlled trial, or to serve as a comparator arm in an externally controlled trial, including historically controlled trials." With the increasing application of external control for single-arm trials, it would be helpful for the final guidance to clarify whether the study to collect external control data is considered part of the interventional study or is still considered a non-interventional study.	FDA should provide clarity regarding whether they are referring to external control trials for untreated vs. actively treated populations. The guidance discusses using RWD to help identify frequency of endpoints, which would typically mean the frequency in an "untreated" population. More clarity should be provided on this. Regarding externally and historically controlled trials, FDA should also provide clarity about whether they are discussing active comparator arms or considering natural history comparators.
Lines 84-103	The draft guidance states, "FDA regulations under part 312 outline procedures and requirements…"	Section 312.23 (a) (viii) requires reporting of contract research organizations that may be involved in the study. The FDA should consider adding additional considerations for data vendors who may also supply data to support non-interventional studies submitted to the FDA for regulatory review. As the FDA is coordinating guidance for RWD standards, it must recognize that many non-interventional studies engage data vendors who supply de-identified data (EHR, Claims, Genomic, Patient reported) sometimes in collaboration with contract research organizations. The FDA must engage the data vendor industry to collaboratively develop best practices and provide guidance for the reporting of data used for regulatory purposes from data vendor companies. Basic

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		elements such as data provenance, data quality, the use of common data models, and data temporality must be considered and evaluated by the FDA as they make regulatory decisions with RWD.
General comment	While the current draft guidance is geared heavily towards studies seeking to establish causal inference, we ask the Agency to take a fit-for-purpose approach to RWD evaluation that is tailored to regulatory decision the RWD is meant to support. For example, it would be helpful for the Agency to clarify any differences in the expectations for RWD that will be used to test hypotheses or target causal estimands vs. data used to provide context or help interpret pivotal trials. Illustrative examples of hypothetical use cases where RWE is intended to be the main evidence for approval vs. supportive information submitted as part of the "totality of evidence" would be welcomed by sponsors.	BIO recommends that the Agency provide a fit-for-purpose approach to evidence that aligns with FDA regulations and guidance on how to meet the "substantial evidence" requirements.
General comment	The draft guidance does not include recommendations regarding regulatory considerations pertaining the use of or incorporation of AI/ML in the identification, aggregation or analysis of RWD.	BIO suggests that the Agency consider providing recommendations on the use of emerging technologies such as AI/ML to reduce regulatory uncertainty for sponsors.
Lines 84-103 **Lines 99-104**	The draft guidance states, "Non-interventional studies analyze data reflecting the use of a marketed drug administered in routine medical practice according to a medical provider's clinical	BIO recommends the following edit: "Non-interventional studies analyze data reflecting the use of a marketed drug administered in routine medical

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	judgment and based on patient characteristics, rather than assignment of a participant to a study arm according to a research protocol." Medical guidelines describe standard of care used in indications that are not always authorized and it is not clear from this section how 21 CFR Part 312 would apply in this case Clarification might be needed for marketed drug used in the course of medical practice, outside the authorized indication.	practice (**including for indications not yet authorized**), according to a medical provider's clinical judgment and based on patient characteristics, rather than assignment of a participant to a study arm according to a research protocol."
Lines 91-97	The draft guidance states, "Interventional studies involving drugs generally meet the definition…" In addition to describing the use of RWD in interventional studies, it may be helpful to also mention trials conducted in routine care settings (i.e. pragmatic trials) in this section since these may generate RWE.	BIO recommends that the Agency consider also mentioning trials conducted in routine care settings (i.e. pragmatic trials) in this section since these may generate RWE.
Section A, Lines 93-97, and Section B. Regulatory Considerations for Non-Interventional Studies	The guidance focuses on regulatory considerations for non-interventional studies. However, FDA acknowledges that RWD may be used in interventional studies. The draft guidance states, "FDA recognizes the potential utility of using RWD in interventional studies…"	BIO recommends that the FDA further expand on regulatory considerations regarding the use of RWD in interventional studies in this draft guidance. BIO also recommends that the Agency consider outlining in this guidance any specific regulatory considerations for when RWD is used in interventional studies (i.e. particularly situations or issues that are not well-covered in existing regulations or guidance focused on traditional clinical investigations)

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	It would be helpful for the Agency to provide more detail on the regulatory considerations regarding the use of RWD in interventional studies.	
B. Regulatory Considerations for Non-Interventional (Observational) Studies		
1. Overview		
Lines 117-125	The draft guidance states, "Although many non-interventional studies involve only the analysis of data…" Though FDA articulated an IND is not required for certain retrospective non-interventional studies, it is not clear if certain prospective designed non-interventional studies require an IND.	BIO recommends that the Agency clarify the IND requirement for prospective designed non-interventional studies. For example, a COVID RWE study designed prospectively (UK's RECOVERY Trial). Here are some notable references of a prospectively designed non-interventional study. • ESMO Perspectives: "Real-world research does not need to replace randomised clinical trials to be recognised as valuable for treatment evaluation" – LINK • RECOVERY Trial paper wins BMJ's 2021 UK Research Paper of the Year Award – LINK • RECOVERY Trial Main Website – LINK • RECOVERY Trial Results, Study Protocol, SAP – LINK ClinicalTrials.gov Identifier NCT04381936: Randomised Evaluation of COVID-19 Therapy (RECOVERY) – LINK
Lines 119-120	The draft guidance states, "…include ancillary protocol-specified activities or procedures (e.g., questionnaires, laboratory tests, imaging studies)…"	BIO recommends that the Agency consider the following edit: "…include ancillary protocol-specified activities or procedures (e.g., questionnaires, laboratory tests, imaging

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		studies**, and data acquisition using digital health technologies**)…"
Lines 110-130	In the draft guidance parts of 21 CFR 314 are referenced. In guidance from 2005 (Guidance on Pharmacogenomic Data Submissions https://www.fda.gov/media/72428/download), the FDA organizes its guidance around Topic areas. In addition, this guidance document presents likely research scenarios, type of submission, and rational for data submission using pharmcogenomic data.	BIO recommends that a similar structure and guidance should be considered as the FDA issues guidance for the use of RWD. Topic areas for consideration can include structure for non-interventional study types such as new indications (disease/illness), new populations, pragmatic trials, single arm control studies, etc.) or any non-interventional studies that use RWD.
2. Transparency Regarding Data Collection and Analysis		
Section 2. Transparency Regarding Data Collection and Analysis	It would be helpful if FDA clarified whether this section applies to *any* non-interventional study intended to support a marketing application (e.g. disease state study to demonstrate unmet need) or whether it is intended to cover studies investigating the drug or a comparator to provide primary or supportive evidence for the marking application.	BIO recommends that the Agency clarify whether this section applies to *any* non-interventional study intended to support a marketing application (e.g. disease state study to demonstrate unmet need) or whether it is intended to cover studies investigating the drug or a comparator to provide primary or supportive evidence for the marking application.
Line 132	Since outcomes in the real-world setting may not be the same, we suggest FDA include a step to evaluate gaps between clinical endpoints in the clinical setting(i.e., PFS, ORR) vs clinical endpoints in the real-world setting (i.e., rwORR, rwPFS).	BIO recommends that the Agency include a step to evaluate gaps between clinical endpoints in the clinical setting (i.e., PFS, ORR) vs. clinical endpoints in the real-world setting (i.e., rwORR, rwPFS).
Line 135	The draft guidance states, "…intended to support a marketing application."	BIO recommends that the Agency clarify that this could apply to marketing application for a new drug or marketing application for a new indication of an already approved drug.

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Lines 134-139	The draft guidance states, "Sponsors should engage with FDA in the early stages…" Similar to other guidance documents it is unclear how/when to engage FDA. The guidance says early, but then says a protocol/SAP is expected. It is unclear if this is a multi-step engagement or if FDA expects that sponsors come to them with a protocol/SAP.	BIO recommends that the Agency clarify if for prospective real-world studies, the case report form (CRF) or similar document should be shared with FDA. BIO also recommends that the Agency clarify the expected pre-reads for the Type C meeting to discuss Agency expectations for the design and conduct of studies, i.e. the consideration of primary/secondary data analysis, cohort/case-control design choices, potential data sources and sample size estimation, as well as the pros and cons of different approaches, etc. Specifically, 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. In addition to the review division, it would be helpful to have representatives from the Office of Surveillance and Epidemiology and the Office of Medical Policy participate in the meeting as appropriate.
Lines 137-139	The draft guidance states, "Sponsors should provide draft versions of their proposed protocol and statistical analysis plan (SAP) for Agency review and comment, prior to finalizing these documents and before conducting the study analyses."	BIO recommends that the Agency provide more clarity on what level of detail is needed in the protocol and SAP to have an effective conversation with FDA.
Line 142	Since patient population in real-world setting is sometime defined differently comparing to those in the clinical trial setting, we suggest the SAP include methodologies of patient	BIO suggest the SAP include methodologies of patient inclusion/exclusion and sensitivity analyses based on relative different patient populations.

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	inclusion/exclusion and sensitivity analyses based on relative different patient populations.	
Line 147	The draft guidance states: "In addition, any revisions to the protocol should be date-stamped, and the rationale for each change should be provided." BIO recommends that the same guidance apply to SAP revisions, too.	BIO recommends the following revision: "In addition, any revisions to the protocol **and/or SAP** should be date-stamped, and the rationale for each change should be provided."
Line 147-148	The draft guidance states, "In addition, any revisions to the protocol should be data-stamped…" Recommending that "***any*** revisions to the protocol" be date-stamped is overly broad and could be onerous.	BIO recommends that the Agency clarify what level of revisions to the protocol would warrant a new date-stamp. BIO also recommends that the Agency clarify whether FDA's review/endorsement is required of any/all revisions to the protocol and/or SAP.
Lines 140-167	In their current form, these four bullet points seem most relevant to non-interventional studies making secondary use of RWD (i.e. where the outcome data are already available and where steps are needed to ensure systematic selection of data sources and patients to ameliorate the risk of selection bias). This may be less of a concern for non-interventional studies planning prospective data generation, although sponsors would still need to evaluate the adequacy of any planned data capture processes.	BIO recommends that the Agency clarify whether the scope of the bullet points included in Section 2 (Transparency regarding data collection and analysis) includes non-interventional studies planning for the prospective generation of real-world data. If this type of study is in scope, the Agency should clarify how the principles outlined in the four bullet points in Lines 140-167 would apply to such studies.

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Lines 145-147	The draft guidance states, "The sponsor should provide evidence that the protocol and SAP were finalized prior to reviewing outcome data of a study and before performing the prespecified analyses." It is currently unclear the type of "evidence" that is recommended by FDA. We suggest a revision be included with at least one example. It is not clear how the sponsor should meet these expectations. Also, if using RWD to create an external control arm for a single-arm study in oncology, prior access to outcome data may be necessary to evaluate the appropriateness of the use of real-world response and real-world progression endpoints in the external control arm, i.e. establish whether these endpoints can be reliably curated from the RWD and whether they display characteristics consistent with corresponding clinical endpoints that would be measured in the single-arm trial. Such an exercise would form part of the assessment of a study's feasibility.	BIO recommends the Agency provide further clarification regarding the type of evidence needed to satisfy this section of the guidance. For example, we suggest a date-stamped protocol and SAP would be sufficient. We suggest a revision be included with at least one example. BIO recommends that the Agency provide examples of acceptable evidence to ensure protocol/SAP are finalized before analyses. BIO recommends that the Agency clarify or provide recommendations on how cases where access to the outcome data is needed for the purposes of outcome validation should be handled.
Lines 150-155	The draft guidance states: "FDA recognizes that access to and evaluation of relevant data sources or databases are important steps in the design of a study and in evaluating a study's feasibility. Evaluations of data sources or databases for study design or feasibility purposes serve as a first step to (1) learn about the suitability of the data source or database to address the	BIO recommends that the Agency provide parameters around what should be included in a "feasibility study" or include a definition in the glossary (such as implementation of a study protocol except for the outcome assessment) and include what analytic activities should be documented/not documented (e.g., data cleaning, derivation of covariates, frequencies of variables, and completeness of variables).

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	research question being posed and (2) estimate the statistical precision of a potential study without evaluating outcomes for treatment arms." The draft guidance emphasizes the value and necessity of conducting "feasibility studies" prior to conducting non-interventional studies, but there isn't much detail as to what constitutes a "feasibility study".	BIO also requests that a similar clarification or reference be made on Line 165.
Line 155	The draft guidance states, "…study without evaluating outcomes for treatment arms." Consider replacing "treatment arms" by "treatment groups" in the context of non-interventional studies.	BIO recommends that following edit: "…study without evaluating outcomes for ~~**treatment arms**~~ **treatment groups**."
Lines 157-162	The draft guidance states, "Sponsors should describe in the study protocol all the data sources…" Describing all of the data sources accessed can be extensive and overly burdensome to the protocol. It is unclear what level of detail is needed in the protocol to describe data sources, nor what is the benefit of describing all the feasibility evaluations or exploratory analyses of every data source considered. The relevance of including such information in the protocol is also not clear. Clarification would be helpful on "all data sources accessed". During selection of an appropriate data source, sponsors may reach out to many data providers, some of whom would provide only a	BIO recommends that Agency clarify the intent for including information on data sources accessed and results of evaluations and analyses. Also, the Agency should consider limiting the information included in the protocol to only that which is necessary. BIO recommends that the Agency provide more guidance on how to best conduct and document feasibility analyses on external data sets. BIO suggests that FDA provide more detail on defining the feasibility work a priori, so it is clear what is being done in its entirety to ensure it does not cross over into the review of outcomes that should not be done in advance. BIO also recommends that the Agency provide examples of essential elements to be included in the description of

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	rough estimate for feasibility and would be screened out at an early stage. It is unclear if FDA would expect documentation of those early explorations as well. More guidance on how to best conduct and document feasibility analyses on external data sets is welcomed. For example, it would be helpful to understand if this paragraph applies when feasibility is conducted as a preliminary study task and results are not yet available at the time of the study protocol development. Suggest that the feasibility assessment be reported in a separate document (rather than included in the study protocol). This document could also describe the plan for database options and the criteria for selection. Feasibility assessment vs reviewing outcome data prior to the SAP/protocol can be a fine line.	feasibility evaluations of other data sources being considered.
Lines 160-162	"FDA recommends that sponsors generate audit trails in their datasets that can track access to and analyses performed on relevant data sources. Sponsors should document all analyses performed on the data during the study design phase, including feasibility evaluations and exploratory analyses".	BIO recommends that the Agency consider a minimum standard criteria for audit trails/related IT technicalities for sponsors to consider in evaluating data vendors or external CROs to ensure full compliance. BIO recommends that the Agency further clarify expectations regarding audit trails to track access and analyses performed on the selected datasets, when datasets are owned by third parties and not directly

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	It is not clear how much 'feasibility' assessment is permitted in selecting an appropriate fit-for-purpose database. The issue is that feasibility assessment may be conducted by a third-party data vendor before the sponsors makes the final decision on fit-for-purpose database for full contract execution with a specific vendor. As per the guidance, the sponsor is held responsible for audit trails and related technicalities that the data vendors should follow.	shared with Sponsors. In addition, we request FDA exercise flexibility regarding the documentation of data sources evaluated for feasibility.
Line 164-167	The draft guidance states, "Sponsors should document all analyses performed on the data during the study design phase…" FDA is requesting documentation for feasibility analysis, choice of final data analytic set and justification that final analysis do not favor a particular study finding.	BIO recommends that the Agency specify which documents are to contain each component of feasibility assessment and analysis (protocol, SAP, study report, all). Further, often RWE studies (data sources and analytic approaches) are the culmination of a long-term research agenda with studies that initially focus on overall patient characteristics and treatment patterns assessments. We recommend that additional guidance be provided specifying the extent of historical documentation to be provided prior to the final study design.
Lines 169-172	The draft guidance states, "Sponsors should describe patient characteristics of the source population (i.e., the population from which the study population is drawn) and the study population (i.e., the population for which analyses are conducted) and note any differences that may impact the final study findings."	BIO recommends the following edit: "Sponsors should describe patient characteristics of the source population (i.e., the population from which the study population is drawn) and the study population (i.e., the population for which analyses are conducted) and note any differences that may impact the final study findings. **A fit-for-purpose approach based on the**

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	The Agency should consider highlighting the spectrum of possible RWE used in regulatory decision making.	**RWD objectives can drive the relevant descriptions of the source and study populations.**"
Line 172	For the same reason stated in the comment on Line 142, we suggest FDA include sensitivity analyses based on relative different patient populations.	BIO recommends FDA include sensitivity analyses based on relative different patient populations.
3. RWD Data Access		
Line 179	Please consider including a possibility to provide FDA access to patient-level data by using a remote access IT structure (e.g., virtual private network / VPN) instead of physically transmitting patient level data sets.	For some healthcare databases, the transfer of data may not be allowed due to national/local data protection regulations. Remote access to this data (incl. appropriate statistical software environment, e.g., SAS) would allow FDA to nevertheless get full access to analytical datasets and programs.
Lines 181-192	It is unclear where FDA is referring to when it expects patient-level data for any RWD to be submitted. For example, it is not clear if this is referring to anonymized analytic data sets used in the study.	BIO recommends that the Agency Clarify what "patient-level data" is referring to. BIO proposes that FDA refers to this as de-identified patient-level data in the analytic data set and not actual patient medical records.
Lines 181-186	The draft guidance states: "In the early stages of designing a non-interventional study intended for use in a marketing application, sponsors should discuss with the relevant review division the expectations regarding access to RWD for their development program. Sponsors must ensure that they are able to submit patient-level data for any RWD that have been analyzed as part of the clinical study included in a	BIO agrees with the draft guidance's recommendation to provide the Agency with patient-level data when using real world data to support a product's effectiveness and safety in a marketing application. There may be situations, however, when the most fit-for-purpose dataset is unavailable for the sponsor to provide directly to the Agency. Whether data are provided by sponsors, data providers, or other third parties, the final guidance should specify a range of options that meet FDA's requirement

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	marketing application when required under 21 CFR 314.50 and 601.2."	for direct access to patient-level data and the recommended processes for providing this access. There can also be instances where variables used in the study are derivatives of unstructured data that are difficult to submit, for instance, a response variable defined based on abstraction on physician notes or pathology reports. In such cases patient-level data may not be readily obtainable. BIO requests that the Agency recommend actions that can be taken to ensure data used is robust in such instances of derived variables. BIO also recommends that the Agency clarify data formatting requirements by linking to the *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* guidance when both are finalized.
Lines 188-191	The draft guidance states, "If certain RWD are owned and controlled by third parties…" This suggestion will limit the use of RWD providers. The proprietary nature of some data sources and the use of tools for anonymization (tokenization) would eliminate large data sources.	BIO recommends that the Agency clarify that the availability and submission mechanisms of patient level data should be discussed with the Agency, if needed, to support the Agency's review of a marketing application. This is important to maximize the use and impact of RWD.
Line 193	The draft guidance states, "Sponsors should ensure that RWD and associated programming codes and algorithms submitted to FDA are documented, well-annotated, and complete, which	BIO recommends that the Agency clarify whether there will be a requirement to submit the raw data as well as programming codes to the FDA. If so, BIO also

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	would allow the FDA to replicate the study analysis using the same dataset and analytic approach."	recommends that the Agency clarify the timing for this submission. BIO recommends the following edit: "Sponsors should ensure that RWD and associated programming codes and algorithms submitted to FDA are documented, **timestamped,** well-annotated, and complete, which would allow the FDA to replicate the study analysis using the same dataset and analytic approach." BIO recommends that the Agency clarify in the final guidance that algorithms necessary to enable FDA to replicate analyses conducted on the final analytic dataset be provided by sponsors, but that any software/algorithms/code that may be proprietary to the data provider (e.g. software used to extract/transform data from source data into the final analytic dataset) be made available for inspection, as applicable. BIO also recommends that the Agency clarify data formatting requirements by linking to the *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* guidance when both are finalized.
Line 195	The draft guidance states: "[…] allow the FDA to replicate the study analysis using the same dataset and analytic approach."	BIO recommends the following revision: "[…] allow the FDA **statistical reviewer** to replicate the study analysis using the same dataset and analytic approach."

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	It would be helpful for FDA to clarify if this is the role of the statistical reviewer.	
4. Study Monitoring		
Lines 199-205	It is not clear in this section what kind of standards of study monitoring FDA expects. For examples, does FDA expect current clinical trial monitoring standards e.g., study visit reports, regular monitoring reports, trail master file, etc.	BIO recommends that the Agency clarify expectations for study monitoring.
5. Safety Reporting		
Lines 217-218	The draft guidance states, "…the Agency requires that relevant adverse events be submitted to FDA…" More detail on what is considered a "relevant AE" and what level of information is to be reported (given information such as relationship to drug or severity may not be available in RWD) would be helpful Some databases do not contain adverse event data. It would be helpful for the Agency to clarify whether they are recommending that sponsors seek additional data (e.g. via chart review) to identify adverse events. The statements in Lines 227-231 suggest that sponsors do not need to actively search for adverse events.	BIO recommends that the Agency provide more detail on what is considered a "relevant AE" and what level of information is to be reported (given information such as relationship to drug or severity may not be available in RWD). BIO also recommends that Agency clarify that they are not recommending that sponsors seek additional data (e.g. via chart review) to identify adverse events as suggested in lines 227-231.
Lines 222-233	The draft guidance states " For example, a larger dataset may contain information regarding a product's approved and unapproved uses in	BIO recommends that the Agency consider providing another example or additional examples beyond using data to support labeling changes.

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	clinical practice. If the sponsor isconducting a study to support a specific labeling change (e.g., a new indication), FDA does not expect the sponsor to search the entire database regarding all uses of the productfor adverse events that would meet the reporting requirements under FDA's postmarketing reporting regulations."	
6. Other Sponsor Responsibilities		
Lines 235-237	The draft guidance states: "For a marketing application containing a non-interventional study submitted to support regulatory decisions regarding the safety or effectiveness of a product, the electronic systems used by the sponsor to manage the data and produce required records must comply with 21 CFR part 11." **The guidance is a commendable attempt at starting to delineate the requirements for observational studies re data collection, analysis, data access and study monitoring.** It will be important to begin addressing details re: data sources / data vendors and feasibility of managing data in electronic systems. It is understood that data used in the marketing application will need to be made available to FDA for their own interrogation similar to clinical trial data. Also, sponsors will need to be able to address queries from the FDA during review,	BIO recommends that the Agency harmonize all of the RWE guidance documents to inform considerations around data sources, data vendors and feasibility of managing data in electronic systems. BIO also recommends that the Agency consider moving this text toward the beginning of the document where the scope of the guidance is described.

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	hence clarity on detailed requirements for available data is essential. The other FDA draft guidances will need to be appropriately tied to this guidance to inform these details.	
Line 242	Suggest adding to the bulleted list: Documenting feasibility and exploratory analyses conducted on the data source(s)	BIO suggests adding the following sub-bullet: **Documenting feasibility and exploratory analyses conducted on the data source(s)**
Lines 248-249	The draft guidance states, "Ensuring that the study is conducted in accordance with the final protocol and statistical analysis plan and documenting any deviations." If this non-interventional study is a retrospective study, should one document (either call it as a protocol or SAP) be sufficient to serve the purpose? Since in clinical trial, "Protocol" is designed to collect data prospectively with collecting procedures specified, that is not applicable in a retrospective study when data were already occurred.	BIO recommends the Agency clarify if this non-interventional study is a retrospective study, whether one document (either call it as a protocol or SAP) be sufficient to serve the purpose.
Lines 256-257	The draft guidance states, "Ensuring appropriate monitoring of the study…" It is unclear what "appropriate monitoring, including (when applicable) selecting a monitor qualified by training" means. Does this suggest ensuring representation of additional relevant expertise (e.g. PRO or labs) in the study team, or something beyond such as independent personnel to monitor the study activities?	BIO recommends that the Agency clarify if this suggests ensuring representation of additional relevant expertise (e.g. PRO or labs) in the study team, or something beyond such as independent personnel to monitor the study activities.

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Lines 271-273	The draft guidance states, "If sponsors engage third parties (e.g., data vendors or contract research organizations) to perform certain study-related tasks, sponsors should document the roles and responsibilities of the organization or organizations performing the tasks." FDA should consider adding academic institutions as an example.	BIO recommends the following edit: "If sponsors engage third parties (e.g., data vendors, contract research organizations, or **academic institutions**) to perform certain study-related tasks, sponsors should document the roles and responsibilities of the organization or organizations performing the tasks."
Line 272-273	The draft guidance states, "…sponsors should document the roles and responsibilities of the organization…"	BIO recommends that the roles and responsibilities of the relevant individuals at the organization(s) are retained and made available as well.
Entire Section		BIO encourages the Agency to consider adding a section in Part B for Data Vendors, since they are commonly contracted by Sponsors and some of the guidance pertains to having direct access to data, transparency on data accrual and other processes under their purview.
IV. GLOSSARY		
Line 287-297	The draft guidance states: "**Externally Controlled Trial**: A clinical trial that compares outcomes in a group of participants receiving the test treatment with outcomes in a group of people external to the trial, rather than to an internal control group consisting of participants from the same trial population assigned to a different treatment or no treatment. The external control arm can be a group of treated or untreated patients from an earlier time in a historically controlled trial (see definition below) or a group of	BIO suggests adding a definition for "contemporaneous (concurrent) control."

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	treated or untreated patients during the same time period but in another setting." "**Historically Controlled Trial:** A clinical trial in which the results of treatment with the test drug are compared with prior experience derived from the natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. A historically controlled trial is a subset of externally controlled trials (see definition above)." Definitions for "Externally Controlled Trial" and "Historically Controlled Trial" are given. BIO recommends also adding a definition for "Contemporaneous External Control" since it is often required when historical data become obsolete.	