

March 9, 2022

Lauren K. Roth
Associate Commissioner for Policy
Food and Drug Administration, Dockets Management Staff
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: ACRO comment submission on Food and Drug Administration [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 Ms. Roth,

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research and technology organizations. Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-man studies through post-approval and pharmacovigilance research. ACRO member companies manage or otherwise support a majority of all FDA-regulated clinical investigations worldwide. The member companies of ACRO advance clinical outsourcing to improve the quality, efficiency, and safety of biomedical research.

ACRO thanks the Agency for releasing this draft guidance on *Considerations for the Use of Real-world Data and Real-World Evidence To Support Regulatory Decision-making for Drug and Biological Products*. ACRO is pleased to provide the following feedback. ACRO would like to provide three general comments, before moving on to specific lines within the draft guidance.

I. General comments:

First, the draft guidance appears to be a summary of FDA's overall approach to the use of RWD and RWE in clinical studies. Detailed guidance on specific aspects of RWD and RWE use is the subject of a series of specific guidance documents in development by FDA. It would therefore be helpful to include in this general summary a description of how all subsequent guidance documents interconnect. This would be beneficial for stakeholders to understand the overall context of the FDA's RWE program. It would be particularly helpful if the FDA would summarize what they consider to be the minimum requirements for various RWD sources to support alignment on what is most important.

Second, the FDA Study Data Technical Conformance Guide v4.8 (September 2021) states that "Sponsors should provide the software programs used to create all ADaM datasets and generate tables and figures associated with primary and secondary efficacy analyses. Furthermore, sponsors should submit software programs used to generate additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable." However, when real world data is captured, a significant number of different algorithms and other computer programs may be used to extract the data and transform it into common data models before it becomes useable for these analyses. It is not clear from the draft guidance exactly which (or which types of) algorithms and programs are expected to be submitted to the FDA in the context of a clinical study based on real world evidence, nor are FDA's expectations for the validation of these various algorithms and programs, and the submission of validation data, clear. ACRO therefore recommends that an additional

section be added to the guidance that specifically addresses the subject of the programs that FDA expects to be submitted, together with FDA's expectations for validation of these programs and for any submission of validation data.

Finally, in a conventional clinical trial conducted under Investigational New Drug (IND) authority, 21CFR312.57 requires that "A sponsor shall retain the records and reports required by this part for 2 years after a marketing application is approved for the drug; or, if an application is not approved for the drug, until 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified." The draft guidance does not address retention periods for the data, records and reports generated in connection with a non-interventional clinical study based on real world evidence that is used for equivalent regulatory purposes. Consequently, ACRO recommends that FDA's expectations for retention are included in the final guidance.

II. Line-Specific Comments:

Lines 134-139:

The current text reads:

Sponsors should engage with FDA in the early stages of designing a non-interventional study intended to support a marketing application. For example, sponsors can request a Type C meeting with the appropriate review division to discuss Agency expectations for the design and conduct of their studies. 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.

Additional context may be addressed through other methods, e.g., white papers, publications, pilot projects, or collaborative efforts. It would be helpful to have a central repository on the FDA website for such documents, and we therefore recommend the additional wording highlighted in bold below:

*Sponsors should engage with FDA in the early stages of designing a non-interventional study intended to support a marketing application. For example, sponsors can request a Type C meeting with the appropriate review division to discuss Agency expectations for the design and conduct of their studies. 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. **Additional information to support sponsors when designing studies using real world data is available at [include location of appropriate web page].***

Lines 157-162:

The current text reads:

Sponsors should describe in the study protocol all the data sources accessed when designing the study, as well as results from feasibility evaluations or exploratory analyses of those data sources. Sponsors should provide a justification for selecting or excluding relevant data sources from the study. FDA recommends that sponsors generate audit trails in their datasets that can track access to and analyses performed on relevant data sources.

The ICH E6(R2) guidance on Good Clinical Practice defines the protocol as "A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol

referenced documents.” Accordingly, we recommend addition of the text highlighted in bold to make clear that the required information can be described in a separate document referenced in the study protocol:

*Sponsors should describe in the study protocol **or a separate document referenced in the protocol** all the data sources accessed when designing the study, as well as results from feasibility evaluations or exploratory analyses of those data sources. Sponsors should provide a justification for selecting or excluding relevant data sources from the study. FDA recommends that sponsors generate audit trails in their datasets that can track access to and analyses performed on relevant data sources.*

Lines 221-231:

The current text reads:

For non-interventional studies, FDA recognizes that sponsors will often use only a subset (often called an analytic dataset) of a larger real-world dataset to conduct their analyses to support labeling changes. For example, a larger dataset may contain information regarding a product’s approved and unapproved uses in clinical practice. If the sponsor is conducting 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 product for adverse events that would meet the reporting requirements under FDA’s postmarketing reporting regulations. Nonetheless, if a sponsor identifies adverse events that are subject to postmarketing reporting requirements during the course of conducting a non-interventional study, such events must be reported in accordance with applicable postmarketing reporting requirements.

We welcome FDA’s flexibility on the need for the sponsor to search the database for adverse events, and recommend addition of the text highlighted in bold to ensure that the study protocol describes the extent of database searching that will be performed to identify adverse events:

*For non-interventional studies, FDA recognizes that sponsors will often use only a subset (often called an analytic dataset) of a larger real-world dataset to conduct their analyses to support labeling changes. For example, a larger dataset may contain information regarding a product’s approved and unapproved uses in clinical practice. If the sponsor is conducting 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 events that would meet the reporting requirements under FDA’s postmarketing reporting regulations. Nonetheless, if a sponsor identifies adverse events that are subject to postmarketing reporting requirements during the course of conducting a non-interventional study, such events must be reported in accordance with applicable postmarketing reporting requirements. **The study protocol should describe the extent of database searching that will be performed to identify adverse events.***

Thank you for this opportunity to provide feedback. Please do not hesitate to contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions.

Respectfully submitted,



Karen Noonan, Senior Vice President, Global Regulatory Policy