Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)

March 2024
Real World Data/Real World Evidence (RWD/RWE)

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Contains Nonbinding Recommendations

Draft — Not for Implementation

Real-World Evidence: Considerations Regarding Non-Interventional Studies for Drug and Biological Products Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance provides recommendations to sponsors and investigators who are considering submitting a *non-interventional study*, also referred to as an observational study, to FDA to contribute to a demonstration of substantial evidence of effectiveness[2] and/or evidence of safety of a drug.[3] Specifically, this guidance discusses attributes regarding the design and analysis of a non-interventional study that sponsors should consider when proposing a non-interventional study for such regulatory purposes.

In this guidance, a non-interventional study is a type of study in which patients receive the marketed drug of interest during routine medical practice and are not assigned to an intervention according to a protocol.[4] Examples of non-interventional study designs for evaluating the effectiveness and/or safety of a drug include, but are not limited to, (1) observational cohort studies in which patients are identified as belonging to a study group according to the drug or drugs received or not received during routine medical practice, and subsequent biomedical or health outcomes are identified; (2) case-control studies in which patients are first identified as

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research and the Oncology Center of Excellence at the Food and Drug Administration.

[2] For more information on demonstrating substantial evidence of effectiveness for applicants planning to file new drug applications (NDAs), biologics license applications (BLAs) or applications for supplemental indications, see the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019). When final, this guidance will represent FDA's current thinking on this topic. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

[3] In this guidance, the term *drug* includes both human drugs and biological products.

[4] In this guidance, in contrast to non-interventional studies, interventional studies (also referred to as clinical trials) are a type of study in which participants, either healthy volunteers or volunteers with the condition or disease being studied, are assigned to one or more interventions with a drug, according to a study protocol, to evaluate the effects of those interventions on subsequent health-related biomedical or behavioral outcomes.

belonging to a study group based on having or not having a health-related biomedical or behavioral outcome, and antecedent treatments received are then identified; and (3) self-controlled studies (e.g., case-crossover[5] and self-controlled case series[6]), where the same person serves as their own control.

The reliability and relevance of real-world data (RWD)[7] used in a non-interventional study[8] are critical for making appropriate causal inferences and are essential to establishing the data's fitness for use in generating real-world evidence to support a labeling change or address a safety concern. When considering RWD, the term reliability includes accuracy, completeness, and traceability;[9] the term relevance includes the availability of data for key study variables (exposures, outcomes, covariates) and sufficient numbers of representative patients for the study. FDA has published guidances addressing corresponding issues related to fitness for use (i.e., reliability and relevance) when using electronic health records (EHRs) and medical claims data as well as data from registries to support regulatory decision-making.[10] The Agency has also published a guidance on considerations for using data standards that are currently supported by FDA in applicable drug submissions containing study data derived from RWD sources.[11] Additionally, FDA published a guidance that describes regulatory considerations for non-interventional studies involving the use of RWD, including RWD access, study monitoring, safety reporting, and other sponsor responsibilities.[12] Two issues discussed in the previously

[5] In this guidance, a *case-crossover study* is a type of non-interventional study design in which study subjects are selected based on experiencing an event of interest (cases), and study subjects serve as their own comparators (controls) during a previous period of time. In this study design, the odds of exposure in the period immediately preceding the event of interest (case period) are compared with those in an earlier period that did not result in an event (control period).

[6] In this guidance, a *self-controlled case series* is a type of non-interventional study design used to investigate the association between a transient exposure and an event of interest. This study design is similar to case-crossover studies, but each case's observation time is divided into exposure (case) and non-exposure (control) periods.

[7] In this guidance, *RWD* are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

[8] Non-interventional studies often repurpose electronic health record-based or medical claims-based data obtained from clinical practice, but a non-interventional design can also include the collection of additional (primary) data. For example, data collection in a non-interventional context when done according to a research protocol (e.g., for a registry) represents primary data collection.

[9] In this guidance, *traceability* is the method (e.g., audit trail) that allows for knowledge of data provenance (i.e., the origin of a piece of data and how it got to the RWD source).

[10] See the draft guidance for industry *Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products* (September 2021). When final, this guidance will represent FDA's current thinking on this topic. See also the guidance for industry *Real-World Data: Assessing Registries To Support Regulatory Decision-Making for Drug and Biological Products* (December 2023).

[11] See the guidance for industry *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* (December 2023).

published guidance are particularly relevant in the design phase of a non-interventional study: the importance of (1) prespecification of study design and conduct and (2) early engagement with FDA to help address the appropriateness of using a non-interventional study design to address the research question of interest for the proposed indication. The topics discussed here should be considered in conjunction with the recommendations in all of these other guidances.

This guidance addresses the growing interest in the potential use of non-interventional studies to support the demonstration of the effectiveness of a drug. FDA has previously published a guidance describing best practices specific to conducting and reporting on pharmacoepidemiologic safety studies that use electronic health care data to assess the risk associated with a drug exposure.[13] The broad epidemiologic principles presented here may also be relevant to pharmacoepidemiologic safety studies.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

The objective of conducting clinical studies of a drug is to distinguish the effect of the drug from other influences, such as spontaneous change in the course of the disease, placebo effect, or biased observation. When relying on a non-interventional study (e.g., EHR data generated during routine clinical care analyzed using a cohort study design), the inference(s) drawn may be incorrect if based on estimates that are affected by (1) confounding (e.g., due to noncomparable treatment groups) or (2) other forms of bias (e.g., how patients are selected for the study, if follow-up periods for assessing outcomes are incorrectly specified, when the accuracy for measuring the outcome is different in exposed and unexposed patients, data on key variables are missing not at random). Identifying and addressing the presence of such confounding and other sources of bias is critical when planning and conducting non-interventional studies. Accordingly, before choosing a non-interventional study design for a study intended to support regulatory decisions regarding the safety and effectiveness of a product, sponsors and researchers should consider how likely it is that such a study design and its conduct will be able to distinguish a true treatment effect from other influences.

The remainder of this guidance assists sponsors in identifying and addressing commonly encountered challenges when considering the use of a non-interventional study for regulatory decision-making, including topics sponsors should consider before developing a prespecified protocol and statistical analysis plan (SAP).

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[12] See the guidance for industry *Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products* (August 2023).

[13] See the guidance for industry and FDA staff *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data* (May 2013).

III. CONSIDERATIONS FOR NON-INTERVENTIONAL STUDIES

A. Overview

This section describes important attributes of a non-interventional study design and analysis that sponsors should consider when using these types of studies to support the demonstration of substantial evidence of effectiveness and/or evidence of safety. Other attributes that are not mentioned in this guidance could also be important for a specific study. FDA strongly encourages sponsors to engage with the Agency in the early stages of designing a non-interventional study and to provide sufficient information needed to clarify expectations related to the design and proposed conduct of their study. Although detailed information on every attribute described may not be available or feasible to include at the time of early engagement with FDA, successful proposals for non-interventional study designs should satisfactorily address each of the elements listed below, as applicable. When the available data sources do not support proposals that can satisfactorily address each of these attributes, alternative study designs should be considered.

B. Summary of the Proposed Approach

Sponsors should finalize the study protocol, including the research question of interest and rationale for the study design, before initiating study conduct. Sponsors should also briefly summarize alternative study approaches and candidate data sources they considered before deciding on the proposed approach and discuss why alternative approaches (e.g., randomized trials, single-arm trials) were not feasible in answering the specific study questions. The discussion should reflect an in-depth understanding of the use of the drug(s) of interest and the outcome(s) of interest, as well as the capture of exposure, outcome(s), and relevant covariates in the proposed study population.

To enable FDA to evaluate proposals for non-interventional studies, sponsors should provide information on each of the study attributes listed below:

- Research question (study objective) and hypothesis
- Rationale for using the proposed non-interventional study design
- Choice of study design (e.g., cohort, case-control, self-controlled)[14]

[14] Additional terms are sometimes used to further describe non-interventional study designs. For example, the terms *prospective* and *retrospective* are commonly but variably used to indicate whether timing of the cause-effect association occurs prior to or concurrent with the investigation that is examining it, whether inferential reasoning is from cause-to-effect or vice versa, whether sample selection is based on exposure or outcome status, or whether a study hypothesis is established prior to or after the corresponding data were collected. These terms are used sparingly in this guidance.

- Proposed selection of data sources to address the study objective and hypotheses, as well as alternative data sources considered

- Results of any preliminary or feasibility studies conducted to assess which data source is fit for use to address the research question being posed and to estimate the statistical precision of a potential study without evaluating outcomes for treatment arms

- Proposed approach to support causal inference (e.g., target trial emulation[15] or other conceptual approach) and to address confounding and other types of bias

- Description of how ethical considerations (e.g., issues related to human subject protection) are addressed.

C. Study Design

Based on the prespecified research question(s) identified, the sponsor should develop study design elements. Each protocol should concisely describe each of the critical elements listed below:

- Schema to describe overall study design as well as a causal diagram[16] to specify the theorized causal relationship

- Source population (i.e., the population from which the study population will be drawn)

- Eligibility criteria and the study population (i.e., the population for which analyses will be conducted)

- Conceptual and operational definitions[17] for key variables of interest and the status of validation efforts for operational definitions, as relevant

- Relevant covariates (e.g., concomitant treatments) and corresponding strategies to address potential bias

[15] Several conceptual approaches can be used to address concerns regarding causality when designing a non-interventional study, including, but not limited to, the emulation of a hypothetical clinical trial that addresses the research question of interest. FDA does not endorse any particular conceptual approach.

[16] Examples of causal diagrams include directed acyclic graphs (DAGs) or single-world intervention graphs (SWIGs). For DAGs, see Greenland, S, J Pearl, and JM Robins, 1999, Causal Diagrams for Epidemiologic Research, Epidemiology, 10(1):37–48. For SWIGs, see Richardson, TS and JM Robins, 2013, Single World Intervention Graphs (SWIGs): A Unification of the Counterfactual and Graphical Approaches to Causality, Working Paper 128, Center for the Statistics and the Social Sciences, University of Washington Series.

[17] In this guidance, *conceptual definitions* explain a study construct (e.g., exposure, outcomes, covariates) or feature in general or qualitative terms; *operational definitions* are the data-specific operation or procedure a researcher followed to measure constructs in a particular study.

- Index date[18] (time zero) for all study arms and the approach to assigning an index date, including strategies to address potential bias introduced by issues related to immortal time[19]

- Start and end of follow-up (at-risk) period, planned approach to censoring, and anticipated losses to follow-up (including depletion of susceptible patients)

D. Data Sources

Sponsors should demonstrate the appropriateness of the proposed data source(s) to address specific hypotheses and research questions. Given that data sources used in a non-interventional study design are often generated for purposes other than research, it is important that sponsors understand the potential limitations of such data sources and determine whether those limitations can be addressed or if another data source should be pursued. Each protocol or accompanying documents should concisely describe each of the elements listed below:

- Description of the proposed data source(s), including how the data were originally collected

- Rationale for choosing the data source(s)

- Relevance of the data to the drug-outcome association of interest

- Appropriateness of the information on relevant confounding factors

- Available information on data reliability (including method of accrual from source data)

- Description of common data models used to provide a standard structure for sharing data from various sources and the rationale behind the choice of the specific model

- Available information on the timing of assessments for key data elements and completeness of these key data elements

- Explanation of how the proposed coding is appropriate based on operational definitions of key variables

- Appropriateness of the data relative to the target patient population

[18] In this guidance, the *index date* (time zero) for follow-up for each participant is the time when they meet the eligibility criteria and are assigned to the intended treatment strategy, which can include no treatment.

[19] In this guidance, *immortal time* is follow-up time in a study during which participants must "survive" to be evaluated for an outcome event.

- Quality assurance activities that will be performed on the extracted original source data

- Existing or potential links to other data sources, as applicable (e.g., merging data from EHRs and claims databases, linking an RWD source to a mortality database to confirm outcomes)

- Plans for additional data collection, as applicable

E. Analytic Approach

The prespecified SAP should address the specific study objectives and detail the primary analysis and any secondary analyses. The plan should include information on each of the elements listed below:

- Assessment of feasibility, including sample size calculation and anticipated operating characteristics (e.g., statistical power)

- Statistical approach or method used to evaluate the treatment effect, including specification of the estimand[20] (e.g., handling of intercurrent events[21] and rules for censoring)

- Specific approach to account for potential confounding factors, including assessment of unmeasured confounding

- Evaluation of potential overadjustment of intermediate variables on the causal pathway

- Approach and rationale for subgroup analyses, as applicable

- Approach to address the potential for unequal detection of outcomes across compared groups (i.e., differential surveillance or differential misclassification)

- Approach to evaluate the potential for early manifestation of the outcome prompting the exposure (i.e., reverse causality)

[20] An *estimand* defines the target of estimation to address the scientific question of interest posed by the study objective (i.e., what is to be estimated). Attributes of an estimand include the population of interest, the variable (or endpoint) of interest, the specification of how intercurrent events are reflected in the scientific question of interest, and the population-level summary for the variable of interest. For further information, see the ICH guidance for industry *E9(R1) Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials* (May 2021).

[21] *Intercurrent events* are events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Intercurrent events should be addressed when describing the clinical question of interest to precisely define the treatment effect that is to be estimated. For further information, see ICH E9(R1).

- Approach to handling missing or misclassified data

- Approach to handling multiplicity (i.e., possible inflation of type I error due to multiple statistical tests, including analysis of multiple exposures or multiple outcomes)

- Description of planned sensitivity analyses, including details on which factors are proposed to be changed and rationale for such changes