
Considerations for the Use of Real-World Data and Real- World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

Guidance for Industry

DRAFT GUIDANCE

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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**December 2021
Real World Data/Real World Evidence (RWD/RWE)**

Considerations for the Use of Real-World Data and Real- World Evidence to Support Regulatory Decision-Making for Drug and Biological Products

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1 **Considerations for the Use of Real-World Data and Real-World**
2 **Evidence to Support Regulatory Decision-Making for Drug and**
3 **Biological Products**
4 **Guidance for Industry¹**
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7 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
8 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not
9 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the
10 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible
11 for this guidance as listed on the title page.
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16 **I. INTRODUCTION**
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18 The 21st Century Cures Act (Cures Act),² signed into law on December 13, 2016, is intended to
19 accelerate medical product development and bring innovations faster and more efficiently to the
20 patients who need them. Among other provisions, the Cures Act added section 505F to the
21 Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355g). Pursuant to this section,
22 FDA created a framework for a program (RWE Program) to evaluate the potential use of real-
23 world evidence (RWE) in regulatory decision-making.³
24

25 FDA is issuing this guidance as part of its RWE Program to satisfy, in part, the mandate under
26 section 505F of the FD&C Act to issue guidance about the use of RWE to help support approval
27 of a new indication for a drug⁴ already approved under section 505(c) of the FD&C Act or to
28 help support postapproval study requirements.⁵
29

¹ This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² Public Law 114-255.

³ See the *Framework for FDA's Real-World Evidence Program*, available at <https://www.fda.gov/media/120060/download>. The framework and RWE Program also cover biological products licensed under the Public Health Service Act.

⁴ For the purposes of this guidance, all references to *drug* or *drugs* include both human drugs and biological products.

⁵ See section 505F(e) of the FD&C Act.

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30 For the purposes of this guidance, FDA defines real-world data (RWD) and RWE as follows:
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- 32 • RWD are data relating to patient health status and/or the delivery of health care routinely
33 collected from a variety of sources.
- 34
- 35 • RWE is the clinical evidence about the usage and potential benefits or risks of a medical
36 product derived from analysis of RWD.
- 37

38 This guidance discusses the applicability of FDA’s investigational new drug application (IND)
39 regulations under part 312 (21 CFR part 312) to various clinical study⁶ designs that utilize RWD.
40 The guidance also clarifies the Agency’s expectations concerning clinical studies using RWD
41 submitted to FDA in support of a regulatory decision regarding the effectiveness and safety of a
42 drug (e.g., as part of a new drug application (NDA) or biologics license application (BLA)) when
43 such studies are not subject to part 312. This guidance focuses primarily on clinical study
44 designs that are non-interventional.

45

46 The contents of this document do not have the force and effect of law and are not meant to bind
47 the public in any way, unless specifically incorporated into a contract. This document is
48 intended only to provide clarity to the public regarding existing requirements under the law.
49 FDA guidance documents, including this guidance, should be viewed only as recommendations,
50 unless specific regulatory or statutory requirements are cited. The use of the word *should* in
51 FDA guidance means that something is suggested or recommended, but not required.

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II. BACKGROUND

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56 For the purposes of this guidance, the term *interventional study* (also referred to as a clinical
57 trial) is a study in which participants, either healthy volunteers or volunteers with the disease
58 being studied, are assigned to one or more interventions, according to a study protocol, to
59 evaluate the effects of those interventions on subsequent health-related biomedical or behavioral
60 outcomes. One example of an interventional study is a traditional randomized controlled trial, in
61 which some participants are randomly assigned to receive a drug of interest (test article),
62 whereas others receive an active comparator drug or placebo. Clinical trials with pragmatic
63 elements (e.g., broad eligibility criteria, recruitment of participants in usual care settings) and
64 single-arm trials are other types of interventional study designs.

65

66 For the purposes of this guidance, a *non-interventional study* (also referred to as an observational
67 study) is a type of study in which patients received the marketed drug of interest during routine
68 medical practice and are not assigned to an intervention according to a protocol. Examples of

⁶ For the purposes of this guidance, the term *clinical study* means research that evaluates human health outcomes associated with taking a drug of interest. Clinical studies include interventional (clinical trial) designs and non-interventional (observational) designs (see section II in this guidance). The fact that this guidance refers to clinical trials as a type of clinical study should not be read to suggest that FDA considers clinical trials to be studies under section 505(o) of the FD&C Act, which authorizes FDA under specific conditions to require postapproval clinical trials and studies.

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69 non-interventional study designs include (1) **observational cohort studies**,⁷ in which patients are
70 identified as belonging to a study group according to the drug or drugs received or not received
71 during routine medical practice, and subsequent biomedical or health outcomes are identified and
72 (2) **case-control studies**, in which patients are identified as belonging to a study group based on
73 having or not having a health-related biomedical or behavioral outcome, and antecedent
74 treatments received are identified.

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77 III. REGULATORY CONSIDERATIONS ADDRESSED

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79 A. Applicability of 21 CFR Part 312

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81 This section discusses the applicability of part 312 (Investigational New Drug Application) to
82 studies involving the use of RWD.

83

84 • FDA regulations under part 312 outline procedures and requirements governing the use
85 of investigational new drugs, including the requirements for an IND submission to and
86 review by FDA. Under § 312.3, a clinical investigation is defined as “any experiment in
87 which a drug is administered or dispensed to, or used involving, one or more human
88 subjects. For the purposes of this part, an experiment is any use of a drug except for the
89 use of a marketed drug in the course of medical practice.”

90

91 • Interventional studies involving drugs generally meet the definition of a clinical
92 investigation under § 312.3 and are subject to FDA regulations under part 312 as
93 described in § 312.2. FDA recognizes the potential utility of using RWD in
94 interventional studies; for example, to identify potential participants for a randomized
95 controlled trial, to ascertain endpoints or outcomes (e.g., occurrence of stroke or other
96 discrete events, hospitalization, survival) in a randomized controlled trial, or to serve as a
97 comparator arm in an **externally controlled trial**, including **historically controlled trials**.⁸

98

99 • Non-interventional studies analyze data reflecting the use of a marketed drug
100 administered in routine medical practice, according to a medical provider’s clinical
101 judgment and based on patient characteristics, rather than assignment of a participant to a
102 study arm according to a research protocol. As such, non-interventional studies are not
103 clinical investigations as defined under § 312.3 and do not require an IND.

⁷ Words and phrases in **bold italics** are defined in the Glossary.

⁸ FDA regulations under 21 CFR 314.126 outlining the characteristics of adequate and well-controlled studies discuss the use of historical controls as comparators in clinical studies. Additional considerations for external or historical controls are addressed in the draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019) (when final, this guidance will represent FDA’s current thinking on this topic) and in the guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001). 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>.

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B. Regulatory Considerations for Non-Interventional (Observational) Studies

This section discusses regulatory considerations for non-interventional studies involving the use of RWD.

1. Overview

- Regardless of a study’s interventional or non-interventional design, the evidence submitted by a sponsor in a marketing application to support the safety and/or effectiveness of a drug must satisfy the applicable legal standards for the application to be approved or licensed.⁹
- Although many non-interventional studies involve only the analysis of data reflecting the use of a marketed drug in routine medical practice, certain non-interventional studies include ancillary protocol-specified activities or procedures (e.g., questionnaires, laboratory tests, imaging studies) that collect additional data to help address questions of interest in these studies. FDA does not consider these types of studies to be clinical investigations under part 312, and an IND is not required. Nonetheless, the protection of human subjects under these circumstances is critical, and sponsors must ensure that applicable requirements per FDA regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards) are met.
- When appropriate, sponsors should consult with experts who consider data privacy issues to provide input on the protocol as part of the study design process for a non-interventional study, as these experts may help identify and address data privacy and security concerns raised when accessing health care data.

2. Transparency Regarding Data Collection and Analysis

- 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.¹⁰ 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.

⁹ See section 505 of the FD&C Act, section 351 of the Public Health Service Act, and 21 CFR parts 314 and 601. Similarly, noninterventional studies may be required by FDA as a postmarketing requirement under section 505(o)(3) of the FD&C Act (or other authorities) or agreed upon between FDA and an applicant as a postmarketing commitment. Such studies carry specific obligations not addressed in this guidance. See, e.g., the discussion of postmarketing requirements and postmarketing commitments in the draft guidance for industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act* (October 2019). When final, this guidance will represent FDA’s current thinking on this topic.

¹⁰ Meeting requests are addressed in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017). When final, this guidance will represent FDA’s current thinking on this topic.

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- To adequately assess the results of a non-interventional study supporting a marketing application, FDA must be confident that particular data sources or databases were not selected, or that specific analyses were not conducted, to favor a certain conclusion. Therefore, the protocol and SAP should be finalized prior to conducting the prespecified analyses listed in the protocol and SAP. 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. In addition, any revisions to the protocol should be date-stamped, and the rationale for each change should be provided.
- 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 research question being posed and (2) estimate the statistical precision of a potential study without evaluating outcomes for treatment arms.
- 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.
- Sponsors should document all analyses performed on the data during the study design phase, including feasibility evaluations and exploratory analyses. Sponsors should also demonstrate that the choice of the final analytic dataset and the conduct of final analyses align with the research question of interest and do not favor particular study findings.
- 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.
- To ensure transparency regarding their study design, sponsors should post their study protocols on a publicly available website, such as ClinicalTrials.gov¹¹ or the web page for the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) for post-authorization studies.¹²

¹¹ See <https://www.clinicaltrials.gov>. For an interventional study that meets the definition of an *applicable clinical trial*, legal requirements exist for submission of certain information relating to the study. See 42 CFR part 11.

¹² See <https://www.ema.europa.eu/en>.

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179 3. *RWD Data Access*

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- 181 • In the early stages of designing a non-interventional study intended for use in a marketing
182 application, sponsors should discuss with the relevant review division the expectations
183 regarding access to RWD for their development program. Sponsors must ensure that they
184 are able to submit patient-level data for any RWD that have been analyzed as part of the
185 clinical study included in a marketing application when required under 21 CFR 314.50
186 and 601.2.
 - 187
 - 188 • If certain RWD are owned and controlled by third parties, sponsors should have
189 agreements in place with those parties to ensure that all relevant patient-level data can be
190 provided to FDA and that source data¹³ necessary to verify the RWD are made available
191 for inspection as applicable.
 - 192
 - 193 • Sponsors should ensure that RWD and associated programming codes and algorithms
194 submitted to FDA are documented, well-annotated, and complete, which would allow the
195 FDA to replicate the study analysis using the same dataset and analytic approach.¹⁴

196 4. *Study Monitoring*

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 - 199 • When a non-interventional study does not include any additional ancillary activities,
200 study monitoring generally may be focused on maintaining the reliability of the RWD
201 and *data integrity*, beginning with extraction of the data from its origin (i.e., data accrual)
202 through data curation and transformation and reporting of results. When a non-
203 interventional study includes additional protocol-specified activities and procedures,
204 study monitoring should also ensure that applicable human subject protections are met
205 and data integrity is maintained.¹⁵
- 206

¹³ For the purposes of this guidance, *source data* include all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation used for reconstructing and evaluating the investigation. For more information, see the guidance for industry *Electronic Source Data in Clinical Investigations* (September 2013).

¹⁴ For additional discussion of data management processes and on maintaining data integrity during data curation and transformation, 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.

¹⁵ See, e.g., 21 CFR 56.111, which includes as a criterion for IRB approval of research that the research plan, where appropriate, makes adequate provision for monitoring data collected to ensure the safety of subjects.

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207 • FDA encourages sponsors to use a risk-based quality management approach to study
208 oversight. This approach focuses sponsor oversight activities on preventing or mitigating
209 important and likely risks to study quality in most instances, and on processes critical to
210 human subject protection that are relevant when ancillary protocol-specified activities or
211 procedures are included in a non-interventional study.¹⁶

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213 5. *Safety Reporting*

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215 • Applicants of NDAs and BLAs and other responsible parties are subject to regulatory
216 requirements regarding postmarketing safety reporting. Given that non-interventional
217 studies examine the use of a drug in routine medical practice, the Agency requires that
218 relevant adverse events be submitted to FDA in accordance with postmarketing safety
219 reporting regulations.¹⁷

220

221 • For non-interventional studies, FDA recognizes that sponsors will often use only a subset
222 (often called an analytic dataset) of a larger real-world dataset to conduct their analyses to
223 support labeling changes. For example, a larger dataset may contain information
224 regarding a product's approved and unapproved uses in clinical practice. If the sponsor is
225 conducting a study to support a specific labeling change (e.g., a new indication), FDA
226 does not expect the sponsor to search the entire database regarding all uses of the product
227 for adverse events that would meet the reporting requirements under FDA's
228 postmarketing reporting regulations. Nonetheless, if a sponsor identifies adverse events
229 that are subject to postmarketing reporting requirements during the course of conducting
230 a non-interventional study, such events must be reported in accordance with applicable
231 postmarketing reporting requirements.¹⁸

232

233 6. *Other Sponsor Responsibilities*

234

235 • For a marketing application containing a non-interventional study submitted to support
236 regulatory decisions regarding the safety or effectiveness of a product, the electronic
237 systems used by the sponsor to manage the data and produce required records must
238 comply with 21 CFR part 11.¹⁹

¹⁶ Additional considerations for risk-based monitoring practices that may be relevant for non-interventional study oversight can be found in the guidance for industry *Oversight of Clinical Investigations—A Risk-Based Approach to Monitoring* (August 2013), the draft guidance for industry *A Risk-Based Approach to Monitoring of Clinical Investigations—Questions and Answers* (March 2019) (when final, this guidance will represent FDA's current thinking on this topic), and the ICH guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).

¹⁷ See §§ 314.80 and 314.81 and 21 CFR 600.80.

¹⁸ *Ibid.*

¹⁹ For further information, see (1) the guidance for industry *Part 11, Electronic Records; Electronic Signatures – Scope and Application* (August 2003), (2) the draft guidance for industry *Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 – Questions and Answers* (June 2017) (when final, this

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- Sponsors who submit non-interventional studies for regulatory review should take responsibility for all activities related to the design, conduct, and oversight of the studies. These activities should include, but not be limited to:
 - Selecting researchers qualified by training and experience to perform study-related activities and confirming that researchers have the skills and information needed to perform their roles in the study
 - Ensuring that the study is conducted in accordance with the final protocol and statistical analysis plan and documenting any deviations
 - Maintaining and retaining adequate study records
 - Ensuring that FDA can access and verify relevant records, such as source records of study analyses (see section III.B.3 of this guidance for data access considerations)
 - Ensuring appropriate monitoring of the study, including (when applicable) selecting a monitor qualified by training and experience for studies requiring additional data collection (e.g., patient-reported outcomes or laboratory assessments)
 - FDA expects that the sponsor will retain and make available to the Agency upon request a log of any researcher or researchers who have significant involvement in the design or conduct of the study. The log should contain information on researchers, including:
 - Researcher’s name and affiliations
 - Description of roles or activities performed
 - Qualifications regarding education, training, and experience to perform the proposed study role
 - 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. These documents should be made available to FDA upon request. Sponsors should remain responsible for all study-related activities unless a sponsor has transferred its responsibility to a contract research organization.

guidance will represent FDA’s current thinking on this topic), and (3) the guidance for industry *Use of Electronic Health Record Data in Clinical Investigations* (July 2018).

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Case-Control Study: A non-interventional study design wherein patients are identified as belonging to a study group based on having or not having a health-related biomedical or behavioral outcome, and antecedent treatments received are identified.

Data Integrity: The property that data or information have not been altered or destroyed in an unauthorized manner, often referred to in terms of the completeness, consistency, and accuracy of data.

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 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).

Observational Cohort Study: A non-interventional study design wherein patients are identified as belonging to a study group according to drug or drugs received or not received during routine medical practice, and subsequent biomedical or health outcomes are identified.