
Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry

DRAFT GUIDANCE

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

**February 2023
Real-World Data/Real-World Evidence (RWD/RWE)**

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1 Considerations for the Design and Conduct of Externally Controlled 2 Trials for Drug and Biological Products¹ 3

4
5 This draft guidance, when finalized, will represent the current thinking of the Food and Drug
6 Administration (FDA or Agency) on this topic. It does not establish any rights for any person
7 and is not binding on FDA or the public. You can use an alternative approach if it satisfies the
8 requirements of the applicable statutes and regulations. To discuss an alternative approach,
9 contact the FDA staff responsible for this guidance as listed on the title page.
10

11 12 13 14 I. INTRODUCTION 15

16 This guidance provides recommendations to sponsors and investigators considering the use of
17 externally controlled clinical trials² to provide evidence of the safety and effectiveness of a drug
18 product.³ In an externally controlled trial, outcomes in participants receiving the test treatment
19 according to a protocol are compared to outcomes in a group of people external to the trial who
20 had not received the same treatment. The external control arm can be a group of people, treated
21 or untreated, from an earlier time (historical control), or it can be a group of people, treated or
22 untreated, during the same time period (concurrent control) but in another setting.^{4,5}
23

24 The guidance addresses considerations for the design and analysis of externally controlled trials
25 to study the effectiveness and safety of drugs, including discussion of threats to the validity of

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 and the Oncology Center of Excellence at the Food and Drug Administration.

² In this guidance, the terms *clinical trials*, *clinical studies*, and *clinical investigations* are interchangeable.

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

⁴ FDA regulations under 21 CFR 314.126 outline the characteristics of adequate and well-controlled studies, and recognize various controls, including a *historical control*, which FDA considers to be a subset of a broader category of potential *external controls*. FDA has accepted various types of external controls, when appropriate, for a specific drug development program. See also the International Council for Harmonisation (ICH) 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>.

⁵ Although multiple arms may be part of the overall trial design, this guidance discusses externally controlled trials involving analysis of a single treatment arm and a single control arm.

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26 trial results from potential ***bias***.⁶ Although various sources of data can serve as the control arm
27 in an externally controlled trial, this guidance focuses on the use of patient-level data from other
28 clinical trials or from ***real-world data (RWD)*** sources, such as registries as well as electronic
29 health records (EHRs) and medical claims.⁷ The guidance also describes considerations related
30 to communicating with FDA and ensuring access by FDA to data from an externally controlled
31 trial.

32
33 This guidance does not address other types of external controls, such as using summary-level
34 estimates instead of patient-level data. This guidance does not discuss details of the design and
35 analysis of a natural history study⁸ nor the reliability and relevance of various sources of RWD⁹
36 that could be used in an externally controlled trial. Finally, this guidance also does not discuss
37 considerations for using external control data to supplement a control arm in a traditional
38 randomized controlled clinical trial.

39
40 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.
41 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only
42 as recommendations, unless specific regulatory or statutory requirements are cited. The use of
43 the word *should* in Agency guidances means that something is suggested or recommended, but
44 not required.

45

46

II. BACKGROUND

47

48

49 The purpose of conducting clinical investigations of a drug product is to distinguish the effect of
50 a drug on the target condition from other influences, such as spontaneous change in the course of
51 the disease, placebo effect, or biased observation.¹⁰ When properly conducted, a clinical trial—
52 with random assignment of participants either to a treatment arm or to a placebo (or other

⁶ Words and phrases in ***bold italics*** are defined in the Glossary.

⁷ Given that an external control arm can involve the use of RWD, FDA is issuing this guidance to satisfy, in part, the requirements of the 21st Century Cures Act to issue guidance on the use of ***real-world evidence (RWE)*** in regulatory decision-making, specifically to evaluate the potential use of RWE to help support the approval of a new indication for a drug already approved under section 505(c) of the FD&C Act or to help support or satisfy postapproval study requirements.

⁸ See 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. Natural history studies can be used for purposes such as identifying a study population, developing clinical outcome assessments or biomarkers, and serving as a comparator group in an externally controlled trial.

⁹ See the following draft guidances 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); *Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products* (November 2021); and *Data Standards for Drug and Biological Product Submissions Containing Real-World Data* (October 2021). When final, these guidances will represent FDA’s current thinking on these topics.

¹⁰ See 21 CFR 314.126(a).

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53 control) arm—optimally promotes the similarity of compared groups regarding such influences,
54 such that a conclusion can be made as to whether differences in outcomes observed between
55 groups can be attributed to the treatment of interest. Nevertheless, for decades FDA has
56 recognized the potential value of other types of controls, including historical controls as a type of
57 external control.¹¹ Clinical trials using these other types of controls can, when appropriate, serve
58 as the adequate and well-controlled clinical investigations generally required to provide
59 substantial evidence of effectiveness under section 505(d) of the Federal Food, Drug, and
60 Cosmetic Act (FD&C Act).¹²

61
62 Given that externally controlled trials do not involve randomization of the study population to
63 the treatments being compared, the treatment and control arm populations should be as similar as
64 possible regarding known factors that can affect the outcome being measured. These factors,
65 discussed in more detail in section III, include important baseline characteristics (e.g.,
66 demographic factors, comorbidities), disease attributes (e.g., severity, symptoms, duration of
67 illness), start of follow-up for the treatment of interest, concomitant therapies, and the clinical
68 observations collected. Importantly, before choosing to conduct a clinical trial using an external
69 control arm as a comparator, sponsors and investigators should consider the likelihood that such
70 a trial design would be able to distinguish the effect of a drug from other factors that impact the
71 outcome of interest and meet regulatory requirements.¹³

72
73 The suitability of an externally controlled trial design warrants a case-by-case assessment,
74 informed by issues including heterogeneity of the disease (e.g., clinical presentation, severity,
75 prognosis), preliminary evidence regarding the drug product under investigation, the approach to
76 ascertaining the outcome of interest, and whether the goal of the trial is to show superiority or
77 non-inferiority.¹⁴ Of note, if the natural history of a disease is well-defined and the disease is
78 known not to improve in the absence of an intervention or with available therapies, historical
79 information can potentially serve as the control group. For example, objective response rate is
80 often used as a single-arm trial endpoint in oncology given the established understanding that
81 tumor shrinkage rarely occurs without an intervention.^{15,16}

82
83 In many situations, however, the likelihood of credibly demonstrating the effectiveness of a drug
84 of interest with an external control is low, and sponsors should choose a more suitable design,

¹¹ See 21 CFR 314.126(b)(2)(v).

¹² See section 505(d) of the FD&C Act (21 U.S.C. 355(d)).

¹³ See 21 CFR 314.126.

¹⁴ A non-inferiority approach is not recommended using an externally controlled trial design. See the guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* (November 2016).

¹⁵ See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001).

¹⁶ See the guidance for industry *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (December 2018).

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85 regardless of the prevalence of disease. For example, when considering whether to use an
86 externally controlled trial design, sponsors should decide whether it is possible to generate
87 evidence capable of distinguishing the effect of the drug from outcomes attributable to the
88 disease’s natural history,¹⁷ prognostic differences in the study populations, knowledge of
89 treatment assignment (lack of blinding), or other factors such as differences in concomitant
90 therapies.

91
92 The remainder of this guidance is intended to assist sponsors in identifying and addressing
93 commonly encountered challenges when considering the conduct of an externally controlled
94 trial.

95

96

97 III. DESIGN AND ANALYSIS OF EXTERNALLY CONTROLLED TRIALS

98

99 A. Design Considerations

100

101 I. Overview

102

103 Reducing the potential for bias in externally controlled trials is best addressed in the design
104 phase, in that well-chosen design elements increase confidence in the interpretability of study
105 results when appropriate analytic methods are applied to estimate treatment effects. Sponsors
106 should finalize a study protocol before initiating the externally controlled trial, including
107 selection of the external control arm and analytic approach, rather than selecting an external
108 control arm after the completion of a single-arm trial. Specific design elements to prespecify in
109 the protocol (i.e., before conducting an externally controlled trial) include suitable study data
110 sources,¹⁸ baseline eligibility (inclusion and exclusion) criteria,¹⁹ appropriate exposure
111 definitions and windows, well-defined and clinically meaningful endpoints, cogent analytic
112 plans, and approaches to minimize missing data and sources of bias.

¹⁷ Scenarios that would not be suitable for externally controlled trials include when the natural history of the disease of interest is not understood sufficiently or when the disease course is considered well-understood but is variable.

¹⁸ FDA recognizes that access to and evaluation of relevant data sources or databases are important steps in designing a control arm for externally controlled trials and in evaluating the trial’s feasibility. Sponsors should document and describe in the trial protocol all data sources accessed when designing the control arm of the trial and the results of any feasibility evaluations or exploratory analyses. Sponsors should provide a justification for selecting or excluding relevant data sources and demonstrate that the choice of a final analytic dataset for the control arm aligns with the research question of interest and was not chosen to favor particular study results. FDA recommends that sponsors generate audit trails in their datasets that can track access to and analyses performed on relevant data sources. See the draft 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* (December 2021). When final, this guidance will represent the FDA’s current thinking on this topic.

¹⁹ In this guidance, the term *eligibility criteria* refers to the requirements for entry into a clinical trial (i.e., the characteristics the participants must or must not have to be able to participate in the trial). See the guidance for industry *Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs* (November 2020).

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113
114 The estimand framework²⁰—involving a precise description of the treatment effect reflecting the
115 clinical question posed by the study objective—can be used to help design an externally
116 controlled trial. An estimand is comprised conceptually of the study population, treatment of
117 interest and comparator, outcome of interest, handling of ***intercurrent events***, and summary
118 measures. Many of the elements of the estimand framework are described individually in the
119 subsections below, and considering the elements together promotes alignment of trial objectives,
120 conduct, analysis, and interpretation of results.

121
122 A specific design consideration for externally controlled trials involves prespecifying plans
123 regarding how to measure and analyze data on important ***confounding*** factors and sources of
124 ***bias***. The ability to identify confounding factors in an externally controlled trial is limited by
125 both conceptual and practical concerns. Conceptually, when seeking to provide evidence of
126 effectiveness using an externally controlled trial design, a thorough understanding is needed—
127 but is often difficult to verify—regarding the natural history²¹ of the disease involved and
128 relevant prognostic factors influencing outcomes. For example, important prognostic factors for
129 an outcome may not be known and therefore cannot be used in the process of developing the
130 external control arm to match, as closely as possible, such factors in the treatment arm.

131
132 From a practical perspective, fit-for-use data on suspected confounding factors (e.g., history of
133 cigarette smoking, performance status) may be missing for some patients or participants or may
134 be measured differently in the external control arm compared to the treatment arm. Accordingly,
135 before deciding whether an externally controlled trial is a suitable design to answer the research
136 question of interest, sponsors should confirm that recognized, important prognostic
137 characteristics can be assessed in the data sources that will be used in an externally controlled
138 trial. Specifically, the source population for the external control arm should be as comparable as
139 possible to the treatment arm population, given that controlling for differences between the two
140 study arms (see section III.C) becomes more challenging with increasingly dissimilar
141 populations.

142
143 Although unmeasured confounding, lack of blinding, and other sources of bias cannot be
144 eliminated in externally controlled trials, an assessment of the extent of confounding and bias,
145 along with analytic methods to reduce the impact of such bias, are critically important in the
146 conduct of such trials. Given the challenges outlined, externally controlled trials are more likely

²⁰ 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 Changes over time in the understanding of the natural history of a disease can also introduce bias in an externally controlled trial. For example, diagnosis of patients with a genetic disorder may have been based historically on the development of signs and symptoms, whereas the development and increased use of genetic testing in clinical trials can diagnose patients at earlier stages of disease (see, for example, EA Nannenber, IAW van Rijsingen, PA van der Zwaag, MP van den Berg, JP van Tintelen, MWT Tanck, MJ Ackerman, AAM Wilde, and I Christiaans, 2018, Effect of Ascertainment Bias on Estimates of Patient Mortality in Inherited Cardiac Diseases, *Circ Genom Precis Med*, 11(10):e001797). In such situations, a historical control arm would have shorter diagnosis-to-death intervals than a treatment arm, even if the drug of interest has no impact on survival.

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147 to provide convincing results when the effect size on a well-characterized outcome of interest is
148 anticipated to be large.²²

149

150 2. *Characteristics of Study Populations*

151

152 In the absence of randomization, a major concern for externally controlled trials is that attributes
153 of patients²³ likely to influence outcomes in an external control arm will differ from
154 corresponding attributes of participants in a treatment arm of the trial. Examples of baseline
155 attributes of participants or patients in treatment and control groups that can be dissimilar include
156 demographic and related factors (e.g., age, sex, race, socioeconomic status, geographic region).
157 Additional attributes that could be dissimilar but often are more challenging to address include
158 disease characteristics (e.g., severity, duration, specific signs and symptoms, performance
159 status), prognostic or predictive biomarkers,²⁴ comorbidities, and prior and current treatments
160 received. When accounting for baseline characteristics, specific challenges can include (1)
161 whether relevant confounding factors are known and well-characterized; (2) whether such
162 confounding factors are captured; (3) whether these factors have been assessed with appropriate
163 methods and measured similarly across compared groups; and (4) whether the study's analytic
164 methods sufficiently address the differences in clinical characteristics between the compared
165 groups.

166

167 A specific consideration involves how well the eligibility criteria can be applied to the external
168 control arm in order to obtain a population comparable to the treatment arm. In addition, unless
169 a concurrent control group is being used, sponsors should consider whether diagnostic criteria for
170 the condition of interest and other relevant baseline factors, or the approaches used to ascertain
171 data on such factors, have changed during the time of data collection. Accordingly, the protocol
172 for an externally controlled trial should include specific plans for evaluating eligibility criteria to
173 determine if the criteria can be applied in a manner that allows for selection of similar patients in
174 the treatment and external control groups, recognizing the limitations of information available in
175 many RWD sources.

176

177 3. *Attributes of Treatment*

178

179 In properly designed and conducted randomized trials, observed differences in efficacy and
180 safety outcomes can generally be attributed to the investigational drug, but confidence in such
181 attribution is diminished in externally controlled trials because of concerns over potentially

²² See the ICH guidance for industry *E10 Choice of Control Group and Related Issues in Clinical Trials* (May 2001) and 21 CFR 314.126(b)(v).

²³ In this guidance, the term *patient* refers to a person whose health care information (e.g., regarding a disease) is included in a study, whereas the term *participant* refers to a healthy person or a person with a disease who participates in a study.

²⁴ Prognostic and predictive biomarkers are used to assess the rate of disease progression or response to therapy, respectively. For additional discussion, see BEST (Biomarkers, EndpointS, and other Tools) Resource, available at <https://www.ncbi.nlm.nih.gov/books/NBK338448>, as well as the guidance for industry *Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products* (March 2019).

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182 important imbalances with respect to treatment between the treatment arm and the external
183 control arm that are either not documented or cannot be accounted for. Such imbalances can
184 involve factors related to the treatment of interest (e.g., adherence, dose, timing of initiation, and
185 duration of treatment) and receipt of additional treatments. These concerns are expected when
186 the data in the external control arm are from an RWD source, and although the remainder of this
187 section focuses on such data sources, potential imbalances can also exist when the data come
188 from other clinical trials.

189
190 Clinical trial protocols typically include a plan for collecting data on use of concomitant or
191 supportive therapies (including non-prescription products) that could affect the outcomes of
192 interest, along with detailed data on the characteristics and administration of such therapies.
193 Examples include drug formulation, dose, strength, route, timing, frequency, and duration—and
194 for certain medications, specific rules for dose modifications, interruptions, or discontinuations
195 are specified in the protocol. In contrast, documentation of such data in routine clinical care may
196 not be complete or accurate, and RWD may therefore lack comprehensive details describing the
197 administration of a treatment or information on the use of concomitant or supportive therapies.
198 For example, suitable data on additional treatment modalities (e.g., radiotherapy and surgical
199 interventions when treating patients with cancer) may not be available in certain data sources. In
200 addition, management of treatment- or disease-related adverse events may not be predefined or
201 described consistently compared to a trial protocol.

202
203 Additional factors can influence the treatment and delivery of care that patients receive as well as
204 the assessment of outcomes related to those treatments when data from clinical care are
205 analyzed. Examples include differences in health-seeking behaviors, insurance coverage
206 (including prescription drug plans), adoption of clinical practice guidelines, availability of novel
207 treatments, and use of companion diagnostic testing (e.g., a genetic test used in conjunction with
208 a corresponding therapeutic product). Access to emergency department or intensive care,
209 availability and coordination of subspecialty care, and academic versus community health care
210 settings can also be markedly different within or across health care systems or geographic areas.
211 These and other health care delivery factors—at the level of the patient, provider, or health
212 system—can influence treatment selection. Such factors should be identified and accounted for
213 adequately in externally controlled trials; otherwise, a different design approach (e.g.,
214 randomized controlled trial) should be considered.

215 216 4. *Designation of Index Date (Time Zero)*

217
218 A specific and difficult challenge when designing externally controlled trials is specifying the
219 index date (also called *time zero* or *zero time*), which is the start of the observation period for
220 assessing endpoints. Given the lack of randomization in externally controlled trials, differences
221 in the way the index date is determined across trial arms may lead to biased effect estimates.
222 The index date for the treatment and control arms in a randomized trial is usually designated as
223 the time when eligibility criteria are determined to have been met and a decision was made
224 regarding the intended treatment strategy for each participant. For an externally controlled trial
225 that relies on RWD, however, the index date for the control arm can be assigned in various ways.

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226 If there are temporal differences in this date relative to treatment initiation or other important
227 landmark times by treatment arm, any observed treatment effects may be biased.

228
229 Determination of the index date in the treatment arm and the external control arm should avoid
230 analyses that include a period of time (immortal time) during which the outcome of interest
231 could not have occurred in one of the two arms. If the index date is not established appropriately
232 across compared arms in an externally controlled trial, bias due to immortal time can occur. For
233 example, consider an externally controlled trial that involves a time-to-event mortality endpoint
234 and an index date established as the time of having failed prior therapy. If analyses of
235 participants in the treatment arm include only those who actually receive the drug of interest,
236 then any period of time between eligibility determination (i.e., failed prior therapy) and treatment
237 initiation is immortal time; that is, the person must survive the period to receive the drug and be
238 accounted for in the analysis. In contrast, if patients in the external control arm do not receive
239 subsequent therapy after determination of eligibility (i.e., failed prior therapy), these patients
240 would be included in the analysis regardless of survival. Accordingly, patients with very short
241 survival times would be included in the control arm but not in the treatment arm, introducing a
242 bias that makes the drug seem more effective than it actually is.²⁵

243
244 When assessing bias that may be introduced related to immortal time in an externally controlled
245 trial, the clinical circumstances related to assigning the index date should be considered.
246 Specifically, if a treatment strategy is assigned immediately after a discrete and identifiable
247 clinical event, the index date for the compared groups may be reasonably determined by the time
248 of occurrence of that event. For example, if treatment is started after an acute myocardial
249 infarction, stroke, or heart failure hospitalization, these events may be more suitable to identify
250 the index date for both the treatment arm and external control arm. In contrast, when the event
251 that prompts the treatment of interest is not discrete and readily identifiable, such as worsening
252 of heart failure symptoms or poor control of hypertension, determining a suitable index date can
253 be difficult or may not be possible. Identifying an index date can also be especially challenging
254 in situations in which no treatment is the treatment strategy for the external control arm.

255
256 *5. Assessment of Outcomes*

257
258 The lack of blinding to treatments in externally controlled trials can pose challenges when
259 considering certain outcomes, in that knowledge of the particular treatment by patients,
260 caregivers, clinicians, or investigators can potentially lead to a biased estimate of the effect of
261 treatment. Accordingly, whenever possible and for suitable endpoints, the outcome should be
262 assessed blinded to treatment status. In some cases, this activity may require re-adjudication of
263 the externally controlled data, such as by blinded independent central review. Bias can also be
264 introduced if outcome assessments in the treatment arm and the external control arm differ based
265 on the sources of data involved or the criteria used to establish outcomes. Sponsors should seek
266 to assess outcomes consistently across the treatment arm and the external control arm for the
267 results of an externally controlled trial to be credible.

268

²⁵ In a randomized trial, potential periods of immortal time are expected to be balanced across treatment groups.

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269 Well-defined, reliable, and clinically meaningful outcomes that are typically used in randomized
270 trials may be particularly difficult to ascertain and evaluate in an RWD source that is being
271 considered for an externally controlled trial. For example, radiologic endpoints in controlled
272 oncology trials (e.g., objective response rate and progression-free survival) are based on
273 prespecified imaging assessment frequency and standardized measurement criteria for response
274 evaluation criteria in solid tumors (RECIST). In routine clinical care, however, radiologic
275 assessment frequency is variable, and formal tumor measurement may not routinely be
276 performed or documented, making a valid assessment of progression-free survival or objective
277 response rate using external control data, such as data from EHRs, challenging.²⁶ A similar
278 consideration applies to the assessment of motor milestones, such as the ability to sit or walk,
279 which are usually not recorded with the same rigor during routine clinical care compared to
280 approaches used in clinical trials. As another example, a randomized trial may include specific
281 testing to detect or confirm a particular clinical entity (e.g., severe inflammatory bowel disease
282 activity confirmed by endoscopy), whereas various strategies may be used in clinical care to
283 identify and confirm the same event. In some cases, and depending on the outcome, the
284 occurrence of an event (e.g., worsening heart failure status according to a specific classification
285 system) may not have been evaluated in clinical care or, if evaluated, may not have been
286 recorded. As a general consideration, outcomes of interest are more likely to be recorded in
287 clinical records when events are objective and/or require immediate medical attention (e.g.,
288 stroke or myocardial infarction).

289
290 When considering outcomes in externally controlled trials, sponsors should also evaluate the
291 consistency of timing of outcome assessments in the treatment arm compared to the external
292 control arm. In general, the timing and frequency of outcome assessments in RWD will have
293 been determined during clinical care²⁷ and may have been influenced by the patient's clinical
294 status, whereas outcome assessments in the treatment arm are protocol-specified. In addition,
295 even when external control arm data are from another clinical trial rather than from an RWD
296 source, the approach to outcome ascertainment may differ from the treatment arm. Accordingly,
297 sponsors should first establish for what total duration of time and at what intervals the outcome
298 of interest should be assessed in the analysis of data from an externally controlled trial. Based on
299 such determinations, sponsors can then evaluate whether the availability and timing of outcome
300 assessments are sufficient and comparable across both arms of the externally controlled trial for
301 the research hypothesis being tested.

302
303 Additional challenges when considering the selection of outcomes to be assessed in an externally
304 controlled trial include changing diagnostic criteria over time for what constitutes abnormal
305 clinical, radiographic, serologic, or other outcomes. Whereas both trial arms would be similarly
306 affected in a traditional randomized trial, extensive heterogeneity or substantial changes in

²⁶ See EA Eisenhauer, P Therasse, J Bogaerts, LH Schwartz, D Sargent, R Ford, J Dancey, S Arbuck, S Gwyther, M Mooney, L Rubinstein, L Shankar, L Dodd, R Kaplan, D Lacombe, and J Verweij, 2009, New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1), *Eur J Cancer*, 45(2):228–247.

²⁷ Registries (one type of RWD) may collect data at predetermined and regular intervals, whereas EHRs and medical claims data would usually not.

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307 diagnostic criteria can introduce bias when analyzing outcomes using a non-contemporaneous
308 external control arm (or when using a reasonably contemporaneous external control arm that
309 reflects a different diagnostic standard of care). As another challenge that can introduce bias,
310 biomarkers used as surrogate outcomes in clinical trials may be used for different purposes in
311 clinical care, or biomarkers used in clinical care may not be well-characterized in terms of
312 comparability to assays used in clinical trials.

313
314 Further challenges may arise from differential capture of intercurrent events that may preclude
315 the measurement of or impair the interpretability of the treatment effect on the outcome of
316 interest. For example, initiation of ancillary therapy after treatment with the drug of interest is
317 started may be protocol-determined and recorded during study visits in a clinical trial, whereas
318 data from routine clinical care may not accurately capture additional therapies, which may
319 confound interpretation of the effect of treatment on the study outcome.

320
321 Other considerations apply when an outcome in an externally controlled trial is based on certain
322 clinical outcome assessments.²⁸ For example, the potential lack of standardization and training
323 in the definitions and use of such assessments in routine clinical care settings—if the assessments
324 are used at all—compared to what occurs in clinical trial settings, can lead to higher variability
325 or bias in the measurements from an external control arm. Accordingly, clinical outcome
326 assessments that are acceptable in randomized trials may not be fit for use in externally
327 controlled trials.

328

B. Data Considerations for the External Control Arm

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1. Data from Clinical Trials

333 Using data from another clinical trial for an external control arm can have advantages compared
334 to using data collected during routine clinical care, based in part on the rigor of protocol-based
335 (and therefore more consistent) data collection. Such use would only be appropriate, however,
336 when comparability exists between the two trial arms regarding participant eligibility criteria,
337 treatment administration, patterns of care (e.g., location of treatment sites), recording of
338 concomitant medications, and assessments of adverse events and outcomes. A particular concern
339 for bias would be the selection of an external control arm from a completed trial whose outcomes
340 are already known. This would be especially problematic if the results of the external control
341 arm are inconsistent with prior experience. Furthermore, when using data from other clinical
342 trials as an external control arm, sponsors should consider the extent of and reason for any
343 missing data and how the interpretability of study results may be affected.

344

345 In many situations, data for the treatment and control arms in an externally controlled trial will
346 have been collected during different time periods. Lack of concurrent data collection may be of

²⁸ A *clinical outcome assessment* is a measure that describes or reflects how a patient feels, functions, or survives. Types of such assessments include measures of *patient-reported outcomes*, *observer-reported outcomes*, *clinician-reported outcomes*, and *performance outcomes*. See BEST (Biomarkers, EndpointS, and other Tools) Resource, available at <https://www.ncbi.nlm.nih.gov/books/NBK338448>.

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347 particular concern when the assessment and management of a disease (including supportive care)
348 changes over time, such as use of predictive or prognostic biomarkers in the patient population.
349 For example, prior trials involving certain cancers may not have information regarding newer
350 biomarkers or specific gene alterations of interest or tumor mutational burden. Accordingly,
351 sponsors should assess whether use of data from a specific clinical trial is justified as an external
352 control arm when planning an externally controlled trial.

353

354 2. *Data from RWD Sources*

355

356 The concerns described in the preceding section regarding comparability of participant
357 characteristics, timing and frequency of data collection, and patterns of care should be addressed
358 when using RWD collected on patients for non-research purposes as external control arms. In
359 addition, specific concerns regarding missing data from RWD sources obtained as part of routine
360 clinical practice can threaten the validity of the results of an externally controlled trial. For
361 example, patients who initially met eligibility criteria may be lost to follow-up (e.g., due to
362 changing their health care provider) from the external control arm. Furthermore, availability of a
363 dataset containing patients with the disease of interest does not guarantee that there is sufficient
364 information on relevant clinical characteristics (e.g., prognostic factors for the outcome of
365 interest) to permit an appropriate comparison.

366

367 3. *Considerations for Assessing Comparability of Data Across Trial Arms*

368

369 The table below summarizes important considerations, discussed above, regarding the
370 comparability of data between the treatment arm and the external control arm. The relevance of
371 each consideration can vary on a case-by-case basis, depending on attributes of the treatment
372 arm, the selected data source for the external control arm, and the stage of the trial (design,
373 conduct, or analysis).

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374 **Table. Summary of Considerations for Assessing Comparability of Data**²⁹
375

Focus of Comparison	Considerations for Data Comparability
Time periods	Various aspects of clinical care may change over time, such as the standard of care for the condition of interest, types of treatments, supportive care regimens, and criteria for determining disease response or progression. Such temporal differences are difficult to address using statistical analyses alone. It is important to consider whether and how different time frames in the treatment arm and the external control arm impact the interpretability of study findings.
Geographic region	Standards of care and other factors (e.g., access to care) that affect health-related outcomes can vary across geographic regions and health care systems. A balance of participants or patients across geographic regions and health care systems in an externally controlled trial, when possible, can help reduce the impact of confounding based on such differences.
Diagnosis	The criteria used to establish a diagnosis may differ based on practice variation or may have changed in the interval between when the treatment arm of the trial was conducted and when the data for the external control arm were collected. Sponsors should consider the diagnostic standards used and whether relevant clinical tests to establish a diagnosis were conducted and reported equally across the compared arms.
Prognosis	Based on demographic and clinical characteristics—and if sufficient knowledge of relevant prognostic factors is available—prognostic indicators for the participants or patients in each arm of the trial should be evaluated and shown to be of sufficient similarity to permit an unbiased assessment of the treatment-outcome association.
Treatments	Attributes of the treatment of interest—including drug formulation, dose, route of administration, timing, frequency, and duration as well as specific rules for dose modifications, interruptions, discontinuations, and adherence—will have been prespecified or measured in the treatment arm. In contrast, specific aspects of a comparator treatment (as applicable) in the external control arm may not have been protocol-driven depending on the data source. Accordingly, sponsors should assess whether the external control arm data can be meaningfully compared to the treatment arm data.
Other treatment-related factors	Various treatment-related considerations, when relevant, include (1) previous treatments received (e.g., lines of therapy in patients with cancer), (2) medications received concomitantly that can affect the outcome of interest, or (3) predictive biomarkers (e.g., genomic testing) related to the treatment of interest. When differentially distributed across groups being compared, such factors can threaten an assessment of the drug-outcome association.
Follow-up periods	Designation of the index date should be consistent between the treatment arm and the external control arm, and the duration of follow-up periods should be comparable across compared arms.
Intercurrent events	The relevance of intercurrent events across treatment arms should be assessed, including differential use of additional therapies after initiation of the treatment of interest.
Outcome	Whether endpoints used in an externally controlled trial can be reliably and consistently measured across the external control arm and the treatment arm will be influenced by several factors, including the definitions of the endpoints, the data

²⁹ Some of the considerations will be relevant to multiple rows.

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Focus of Comparison	Considerations for Data Comparability
	source for the external control arm, and the potential for the outcome to be influenced by knowledge of treatment received. In addition, sponsors should be able to apply the same criteria for the evaluation and timing of outcome assessments across both arms of the externally controlled trial.
Missing data	The extent of missing data in the external control arm should be assessed before conducting an externally controlled trial to evaluate feasibility (when such data are available). When analyzing results from such a trial, the extent of missing data in both the treatment and external control arms should be assessed to examine the potential impact of missing data.

376
377 The considerations listed in the table above are directed at understanding and managing potential
378 threats to the validity of externally controlled trials. Additional considerations regarding the
379 comparability of trial arms may be relevant for a specific externally controlled trial.
380

C. Analysis Considerations

1. General Considerations

384
385 Before conducting an externally controlled trial, sponsors should develop a statistical analysis
386 plan that prespecifies analyses of interest, such as analyses of primary and secondary endpoints,
387 calculations of statistical power and sample size, and plans to control the chance of erroneous
388 conclusions (e.g., to control the overall type I error probability). The statistical analysis plan
389 should be submitted along with the protocol to the relevant review division before initiation of
390 enrollment in the clinical trial for the experimental treatment. In addition, decisions regarding
391 the study design and statistical analysis plan for an externally controlled trial should be blinded
392 to any observed external control data (e.g., from an existing RWD source), with the exception of
393 planned feasibility analyses, such as evaluating the availability of key variables or missing data.
394 During the conduct of an externally controlled trial, and specifically when analyzing data already
395 collected, changes to the statistical analysis plan are discouraged. If such changes are
396 nonetheless implemented, any revisions should be date-stamped and the corresponding rationale
397 provided and discussed with the relevant FDA review division.
398

399 FDA does not recommend a particular approach to analyzing data from externally controlled
400 trials. No single statistical or analytical method will be suitable for all trials involving external
401 control arms, and potential approaches should be discussed with the appropriate FDA review
402 division. Sponsors should provide a justification for the analytic methods selected as well as a
403 description of the strengths and limitations of the methods used to assess the effect of treatment.
404 In general, the analytic method used should identify and manage sources of confounding and
405 bias, including a strategy to account for differences in baseline factors and confounding variables
406 between trial arms.

407
408 Various statistical methodologies may be appropriate for these types of comparisons, each with a
409 corresponding level of complexity regarding approaches to account for bias. The assumptions
410 involved should be made explicit, and sensitivity analyses as well as model diagnostics should be

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411 conducted to examine such assumptions. Importantly, however, adding complexity to an
412 analytical framework usually requires making additional assumptions, which often cannot be
413 substantiated and may impair the interpretability of results.

414
415 Even when employing analytic methods to balance the trial arm populations, sponsors should
416 propose additional analyses to evaluate the actual comparability between the external control and
417 treatment arms for important covariates. Determining similarity across trial arms will require
418 selection of specific population characteristics to compare, a method for the comparison, and
419 criteria to demonstrate similarity. For example, an a priori threshold³⁰ could be set to determine
420 whether the external control population has a statistical distribution of covariates that is similar
421 to the treatment arm population after a balancing method, such as weighting, has been applied.

422
423 Consideration should also be given, based on available scientific data, to the anticipated effect
424 size for analyses of the primary endpoint. Especially when the anticipated effect size is modest,
425 an externally controlled trial may not be an appropriate study design because of concerns for bias
426 affecting the results. In addition, sponsors should develop a priori plans for assessing the impact
427 of confounding factors and sources of bias, with quantitative or qualitative bias analyses used to
428 evaluate these concerns. Such prespecified analyses can assist in the interpretation of study
429 results.

430
431 **2. *Missing Data***

432
433 The proposed analytical methods should include a strategy for dealing with missing data,
434 including data that may not be available in a chosen data source based on the type and frequency
435 of assessments conducted during the patient encounter, patients no longer being followed, or
436 other reasons. Analytical methods (such as strategies for imputing missing data) may be used in
437 such situations, but these methods require assumptions regarding the pattern of missing
438 information.³¹ Assumptions about missing data can be unverifiable and may be difficult to
439 justify, in addition to other assumptions required for estimation of treatment effect in a non-
440 randomized setting.

441

³⁰ FDA does not endorse a single approach for determining thresholds. As one example, a threshold value could be selected for standardized mean differences as a metric that summarizes the statistical distribution of important prognostic covariates.

³¹ The terms *missing completely at random*, *missing at random*, and *missing not at random* describe assumptions about why data are missing. When observations of a variable are *missing completely at random*, the missing observations are a random subset of all observations, such that the missing and observed values have the same underlying distributions, and bias from missing data is not a threat to the study. *Missing at random* indicates systematic differences may exist between the observed and unobserved values of a variable, but other observed variables could be used to address such differences and mitigate bias. *Missing not at random* indicates that the missing data are directly related to the treatment or outcome under investigation, and bias can be introduced. See AR Donders, GJ van der Heijden, T Stijnen, and KG Moons, 2006, Review: A Gentle Introduction to Imputation of Missing Values, *J Clin Epidemiol*, 59(10):1087–1091.

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442 To understand the potential impact of missing data, externally controlled trials should be
443 designed to capture and analyze information relevant to the missing data (e.g., available
444 characteristics of patients with and without missing data). Analytical methods may be used, as
445 mentioned above, to address potential bias caused by the missing data in the primary analysis. In
446 addition, sensitivity analyses should be used to evaluate the potential impact of plausible
447 violations in missing data assumptions on the results of the primary and other key analyses.
448

449 In some cases, data may be missing because of an intercurrent event, which may interfere with
450 the measurement of outcomes and estimation of the treatment effect. The study analysis plan
451 and an appropriate estimand should account for any intercurrent event that can be considered
452 potentially related to both the treatment and outcome of interest, recognizing that certain
453 intercurrent events may be difficult to detect in external control datasets. For example, in
454 contrast to data collected according to a research protocol, RWD sources may not capture the
455 time of occurrence of an intercurrent event, precluding accurate assessment of time-to-event
456 endpoints such as progression-free survival.
457

3. *Misclassification of Available Data*

459
460 Misclassification³² (mischaracterization) of data in externally controlled trials, especially in an
461 external control arm using RWD sources, can occur when the value of a measurement is assigned
462 to an incorrect category for subsequent analysis, potentially affecting estimates of the observed
463 drug-outcome association. For example, EHR data collected during routine clinical care may
464 include information on lifestyle characteristics, such as alcohol use. Beyond concerns about
465 potentially inaccurate reporting by patients about their alcohol intake because of stigma or other
466 factors, differences in the approach used to classify alcohol use within or across various sources
467 of data can lead to misclassification. In routine clinical practice, for example, different health
468 care providers may use different quantitative or qualitative descriptions of alcohol use, such that
469 two patients with the same actual intake may be assigned to two different categories in the RWD
470 source.
471

472 If misclassification is extensive—especially when information on treatments, outcomes, or
473 confounding factors are involved—a biased assessment of the drug-outcome association may
474 occur. For example, the scenario described above regarding misclassification of alcohol intake
475 would be relevant when alcohol use is a potentially important confounding factor (covariate) in
476 an analysis of an externally controlled trial. Although analytical modeling methods could be
477 used to assess the potential impact of misclassification, the best strategy to avoid bias is to use
478 objective and reliable measurements for the data of interest. For example, RWD sources that
479 include information on alcohol intake collected using structured questionnaires are generally
480 more reliable than patient-reported and clinician-documented values obtained during routine
481 patient care.

³² Misclassification errors can be non-differential when the probability of misclassification is equal across study arms or differential when the probability of misclassification differs across study arms. Misclassification can introduce bias regarding the drug-outcome association when involving the drug of interest, covariates, or outcomes of interest.

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4. *Additional Analyses*

Sponsors can also use specific sensitivity analyses to test the vulnerability of trial results to assumptions in the analysis plan. For example, if the primary analysis of a time-to-event endpoint assumes proportional hazards, an appropriate sensitivity analysis could be estimation by a statistical method that does not assume proportional hazards. Finally, prespecified supplementary analyses can provide further understanding of the treatment effect. An example would be supplementary analyses in prespecified subgroups based on prognostic factors for the outcome.

IV. CONSIDERATIONS TO SUPPORT REGULATORY REVIEW

A. Communication with FDA

Sponsors should consult with the relevant FDA review division early in a drug development program about whether it is reasonable to conduct an externally controlled trial instead of a randomized controlled trial. As part of these discussions, sponsors should provide a detailed description of the (1) reasons why the proposed study design is appropriate, (2) proposed data sources for the external control arm and an explanation of why they are fit for use, (3) planned statistical analyses, and (4) plans to address FDA’s expectations for the submission of data.

B. Access to Data and Documents

Sponsors must include in their marketing applications relevant patient-level data (i.e., data on each participant and patient in the externally controlled trial), as required under FDA regulations,³³ for both the treatment and external control arms. If sponsors do not own the data used for the external control arm, they should structure their agreements with the data owners to ensure that patient-level data can be provided to FDA in support of the marketing application. Sponsors should also ensure that FDA has access to *source documents* and *source data* for the external control arm as part of an FDA inspection or upon request.³⁴

³³ See 21 CFR 314.50(f) and 601.2.

³⁴ See the guidances for industry *Use of Electronic Health Record Data in Clinical Investigations* (July 2018) and *Electronic Source Data in Clinical Investigations* (September 2013).

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GLOSSARY

Bias: Any systematic error in the design, conduct, analysis, or interpretation of a study that results in an erroneous estimate of a treatment’s effect on the outcome of interest.

Confounding: Distortion of the measure of the effect of a treatment on an outcome due to another factor that is associated with both the treatment and the outcome.

Intercurrent Event: An event occurring after treatment initiation that affects either the interpretation or the existence of the measurements associated with the clinical question of interest. Examples include switching or discontinuing treatment, using rescue medications, or experiencing terminal events such as death.

Real-World Data (RWD): Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE): Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities (in a clinical investigation) used for the reconstruction and evaluation of the study. Source data are contained in source documents (i.e., original records or certified copies).³⁵

Source Documents: Original documents, data, and records (e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subjects’ diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives; microfilm or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at the medico-technical departments involved in the clinical trial).³⁶

³⁵ See the guidance for industry *Electronic Source Data in Clinical Investigations* (September 2013).

³⁶ See the guidance for industry *E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1)* (March 2018).