



# Considerations for regulatory application of RWD-generated external comparators

**Debra A. Schaumberg, ScD, OD, MPH; and K. Jack Ishak, PhD**

Properly designed and analyzed external comparators (ECs) built from real-world data (RWD) and the resulting real-world evidence (RWE) can be compared in certain situations with data generated from single-arm or traditional randomized clinical trials to support regulatory decisions. Proper development, design, and use of ECs requires more than simple matching of the clinical trial inclusion and exclusion criteria within the RWD source. A focus on the specificity of the research questions, clinical and investigational product context, underlying causal frameworks, and a deep understanding of RWD provenance, granularity, structure, and curation should be carefully considered to ensure a suitable RWD-constructed EC can be designed and a robust comparison is possible to support regulatory decision making.

## **Introduction**

Spurred by the congressional mandates in the 21st Century Cures Act<sup>1</sup> and 6th Prescription Drug User Fee Act,<sup>2</sup> the improving quality and availability of real-world data (RWD), and methodological advances in pharmacoepidemiology, the

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US Food and Drug Administration (FDA) and other medical product regulatory bodies are considering use of real-world evidence (RWE) in regulatory decision making. To that end, the FDA's Real-World Evidence Program, released in December 2018, provides a framework for the agency's multifaceted approach to the evaluation of RWE, with the expectation of the development of guidance documents to further assist sponsors with the use of RWD to develop RWE to support agency regulatory decisions.<sup>3</sup> Existing guidance documents with relevance to the use of ECs focus on using data from electronic health records for clinical investigations<sup>4</sup> and provide guidance on submitting documents using RWD and RWE.<sup>5</sup> As the FDA has already incorporated use of RWE into product safety evaluations (e.g., through the now well-established Sentinel System), the initial focus of the framework is on RWE use cases for demonstration of product effectiveness, including discussion of nonrandomized, single-arm trials with ECs generated using RWD, as well as on postapproval applications, such as label extensions and comparative effectiveness evaluations. The European Medicines Agency and Health Canada also have expressed interest in considering RWE to support regulatory decisions.<sup>6,7</sup> In addition, other medical product regulatory bodies, such as the China Center for Drug Evaluation, have published draft guidance on use of RWE to support drug development.

Although the randomized controlled trial (RCT) remains firmly entrenched as the gold standard for satisfying the regulatory requirement for a well-controlled study, situations arise in some clinical development programs for which RCT can be challenging, unethical, or highly inefficient. In such situations, sponsors often seek to support regulatory submissions with single-arm trials, or traditional RCTs with higher treatment to control allocation ratios. This occurs, for instance, in very rare indications or when early-phase results reveal large benefits, raising ethical concerns about delaying regulatory submissions. Such programs are often granted a special status for accelerated approval pathways in which decisions must be made without the benefit of a traditional RCT. ECs can be implemented alongside these trial designs to provide comparative results and boost robustness of trial findings for efficacy and safety.

The use of ECs for regulatory approval of medical products dates back to at least 1987.<sup>8</sup> ECs are defined broadly in the regulatory context to include both individual subject-level data and comparisons, as well as summary-level data and comparisons of historic trials, natural history, registry data, and other various sources (**Figure 1**). The term external control arm (ECA) comprises a specific type of subject-level EC data in which a cohort of "control" subjects is created outside the trial. The ECA may be constituted from data from control (e.g., placebo arm) subjects from a previously completed RCT, or from various sources of RWD, such as databases, registries, medical record review, or prospective data collection. ECAs can be used for direct comparisons to quantify relative effect sizes or used to benchmark expected outcomes with the comparator (without quantifying a difference).

To date, examples for RWD-based ECs have occurred primarily in the settings of oncology and rare diseases, in which the supportive RWE has typically consisted of ECs using historic response rates based on RWD from chart reviews or

expanded access programs and analyzed separately from the trial as a benchmark for comparison. In the US, the FDA’s framework for its RWE program includes a three-pronged approach to evaluation of RWE for regulatory decisions that considers whether the RWD are fit for use; the RWE provides adequate scientific evidence to answer regulatory questions; and the study conduct meets regulatory requirements.<sup>3</sup> In addition, the FDA has published a number of guidance documents that discuss external comparators and can be useful resources for sponsors seeking to implement a RWD-constructed ECs in the regulatory context.<sup>9-13</sup>

RWD can comprise data from existing claims and/or electronic health record databases, bespoke data collection through medical record review and data abstraction, disease or product registries and other prospective observational studies, and patient-generated health data.

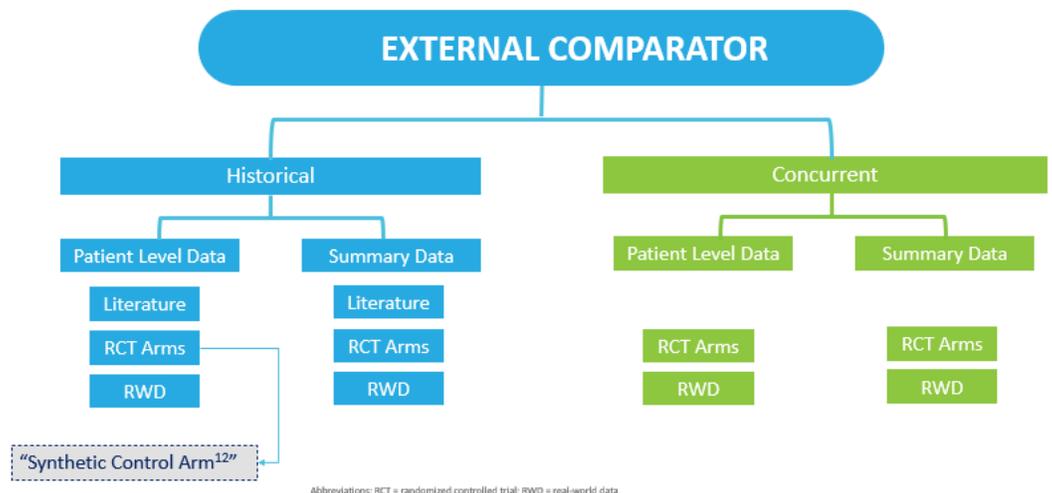
The objective of this paper is to discuss how RWD-constructed ECs may contribute to evidence packages to support initial regulatory approval and effectiveness labeling changes for marketed products, and the regulatory considerations for these actions.

**ECA planning starts with a clear framework for causal inference**

***Purpose of a control group***

The control group experience serves to help us understand what would have happened to patients if they had not received the test treatment or if they had received a different treatment known to be effective, often referred to as the “standard of care.” One way to conceptualize this is to think of a counterfactual world in which one could treat a group of patients with the investigational treatment, and at the same time (e.g., in, say, a parallel universe) instead treat that same group of patients with the control treatment (e.g., placebo, or standard of care; **Figure 2a**). Obviously, this is not tenable, and researchers are consequently challenged with designing a study that minimizes the possibility of bias and maximizes the chance of observing the true benefit versus risk of a

**Figure 1 Common types of data sources for external comparators**



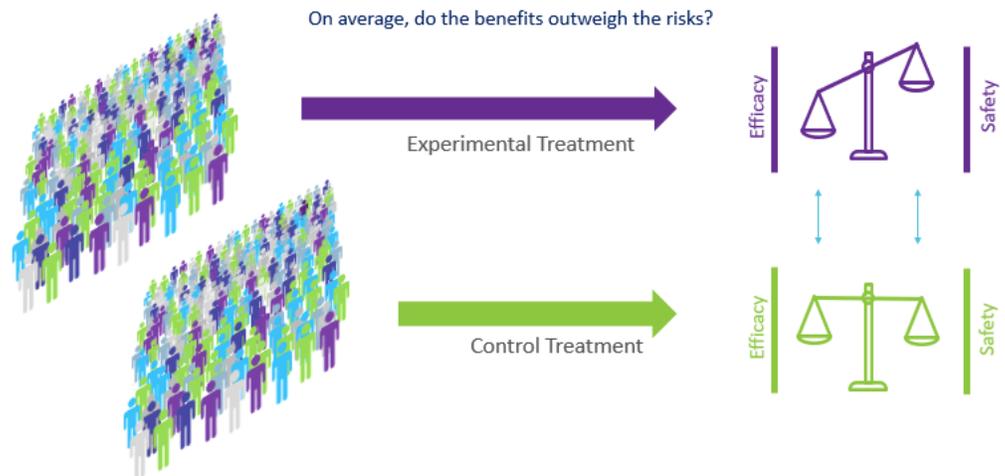
product, allowing discrimination of patient efficacy and safety outcomes caused by the investigational treatment from outcomes caused by other factors, such as the natural progression of the disease, observer or patient expectations, or other treatments.

**Gold standard RCT**

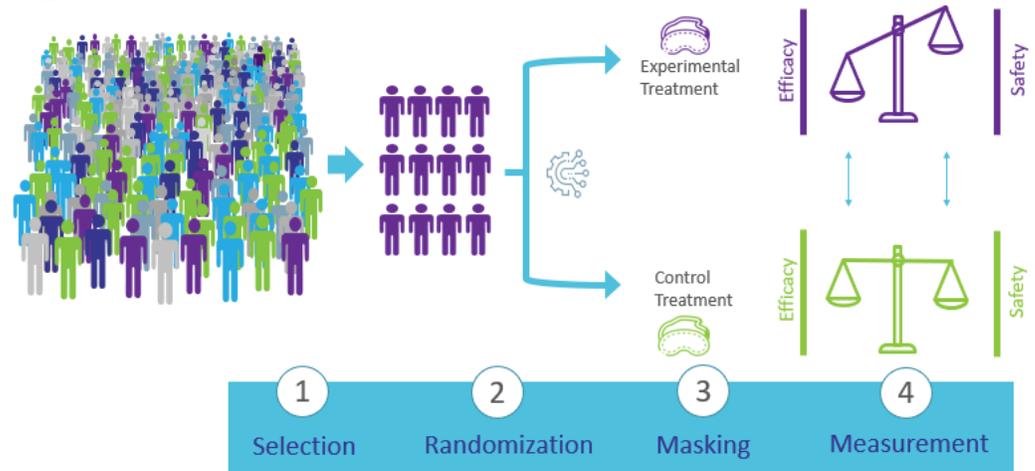
Due to established bias-minimizing design features, the double-masked RCT has emerged as the clear “gold standard” for clinical development programs for new product applications to regulatory authorities. The purpose and impact of the four main bias-reducing elements of RCT design – patient selection, randomization, masking, and measurement – should be understood and addressed with strategies to minimize bias in the design of an ECA (Figure 2b).

**Figure 2 Building a valid ECA starts with a clear framework for causal inference**

**a. Counterfactual paradigm**



**b. Elements of a traditional RCT that enable causal inference**



**Selection.** Most RCTs submitted to regulatory bodies have long lists of very specific inclusion and exclusion criteria that are put in place for several possible reasons, including protecting patient safety, minimizing heterogeneity, and targeting a specific patient profile. Often, the trial inclusion/exclusion criteria contain several measures that are not typically performed in standard clinical care of patients, or variables that are not well captured within structured data in electronic health records (EHR).

In designing an EC, the inclusion/exclusion criteria of the single-arm trial or traditional RCT are ideally matched exactly, however, this is almost always a challenge to implement, not only because of the element of missing measures in RWD, but also because of differences in quality of measurements versus the standardized clinical trial environment. Especially if the trial is being designed in parallel with the ECA, each criterion should be interrogated to justify its inclusion and to understand the extent to which each may influence the outcome of the trial, and consideration should be given to streamlining inclusion/exclusion criteria to enhance comparability with the ECA. In addition, these considerations will weigh into the evaluation of the fitness of potential data sources to provide adequate data to support the ECA. Data from controls selected from previous RCTs may sometimes be preferred, but availability is typically limited to distinct situations in which historic data from past trials are still relevant and accessible. RWD sources (registries, databases, chart reviews, etc.) differ in their mix of strengths and limitations and must be evaluated for use in ECA in each specific context.

**Randomization.** In the traditional RCT, randomization serves to balance treatment groups for patient baseline characteristics that may influence treatment outcomes and accordingly, is an effective means to control for both measured and unmeasured confounding, resulting in a condition of “exchangeability” of the treated and control groups.<sup>14</sup> However, it is often overlooked that randomization achieves these goals only if the sample size of the trial is sufficiently large. The degree of residual confounding is inversely proportional to the sample size of the trial; the larger the sample size, the less likely confounding will significantly affect the trial, and the more likely that randomization will accomplish the desired goal. In contrast, with small sample sizes, which often occurs in trials in rare indications for which ECAs are more likely to be considered, randomization may not fully balance treatment groups and therefore the possibility of confounding remains. Although it may be possible to address confounding by measured variables in the analysis of the resulting trial data, the issue of possible bias from unmeasured confounders remains a concern. These same issues need to be addressed in designing an ECA, where the goal is to attempt to use a set of design features that will best balance the distribution of baseline characteristics between the ECA and the investigational treatment arm of the target trial.

**Masking.** In a traditional RCT, masking of both patients and investigators to the randomized treatment assignment minimizes bias that could arise from differences in patient management, in clinical outcomes assessment, and in patient-reported outcomes (PROs) that could arise if treatments are known. In

contrast, ECAs are most commonly considered in the setting of a single-arm treatment trial, in which a group of patients who have met the inclusion/exclusion criteria all receive the same, open-label treatment known by the investigator, the patient, and the patients' other caregivers.

In this setting, it is important to consider the extent to which knowledge of using the experimental treatment affects the patient outcomes, and typical tactics include the use of quantitative "hard" clinical endpoints that are less likely to be subject to bias. The same considerations are needed for the ECA. If RWD are being used to construct the ECA, patients and doctors were clearly aware of their treatment status, however, the impact of knowledge of a standard-of-care treatment would typically have less of an impact on biasing outcomes than knowledge of receipt of an investigational therapy. Careful consideration is needed during the design of both the trial and the ECA to mitigate the potentially disparate impact of unmasked designs on both safety and efficacy outcomes in the single-arm trial versus the ECA.

**Measurement.** RCTs typically go to great lengths to standardize the conduct and timing of clinical and patient outcome measures, and to train investigators in the conduct of the study procedures. This is aimed at increasing the precision and decreasing the variability of measures for both the ascertainment of inclusion/exclusion variables to define the trial population, as well as the assessment of clinical, laboratory, and PROs. In an RWD-constructed ECA, some of the measures used in the trial may simply not be available in the RWD, or, if they are available, will have been ascertained in standard clinical practice and not subject to the same level of rigor that is typically applied in the target trial. In addition, timing of measurements in RWD will vary to a greater extent than in the RCT.

The inclusion/exclusion criteria for the single-arm trial are often not factors or variables measured in routine clinical practice, so granular one-to-one matching is often impossible, and frequency matching on available baseline factors is still likely to result in residual confounding. This complication, coupled with variations in standard of care, means one should select a larger sample group from a combination of chart reviews and EHR. Although the larger group is less efficient, it also leads to the potential formation and subsequent evaluation of subgroups. Such differences in the availability and timing of measures for RWD-constructed ECAs are the rule rather than the exception and may occur even in indications for which there is a well-defined standard of care. ECAs based on previous RCT control groups are, in theory, less likely to suffer from this limitation. Selection of the most appropriate source of data at the design of the ECA should aim to match the trial measures and carefully define time windows as closely as possible.

#### **Framework for approaching ECA development**

##### ***Understanding the clinical and regulatory context***

ECA development builds on a solid foundational causal inference framework, as well as a clear understanding of the clinical and regulatory context. ECs have typically been considered in the regulatory context in cases for which there are

ethical, operational, or resource considerations that challenge a sponsor's ability to conduct a traditional RCT. These situations most commonly arise in the setting of rare diseases, and more recently in rare oncology indications, for which there is a limited patient population size and/or lack of clinical equipoise, for example, due to high unmet medical need and early data suggesting a large clinical benefit of the investigational treatment. Evaluation of whether an EC may be appropriate will bring together clinical knowledge, an assessment of equipoise, and regulatory intelligence as to when an EC might be appropriate to satisfy the requirements of a regulatory submission. Additional considerations are brought to bear when an RWD-generated EC is contemplated, including feasibility of the RWD approach based on an evaluation of data quality, granularity, and availability of necessary variables.

### ***Purpose of the external comparator***

There are two general types of ECs:

- A benchmark or context-setting EC, in which the trial and EC (often comprised of aggregate, summary-level data) are analyzed separately, and the results compared qualitatively to contextualize the findings of the trial; or
- A direct, hypothesis testing EC, in which individual patient-level data from the trial of the investigational product and patient-level data from an EC are analyzed together and specific hypotheses are evaluated through statistical comparisons.

Benchmark ECs can be constructed after, during, or often before trial initiation, where they can help inform the trial design. Direct, hypothesis-testing ECs usually require larger sample sizes and more granular patient-level data to facilitate direct statistical comparisons with the trial data and can only be done once the trial data are available for joint analysis.

### ***Design of the ECA***

The study design is the foundation for causal inference, and for observational study designs using secondary RWD, there is increased risk of systematic bias that threatens valid inference. Although statistical techniques are available to help adjust for confounding and other sources of bias, the best approach to guarding against such bias is at the design stage of the study. In fact, some forms of bias cannot be adequately addressed with statistical methods, such as when misclassification arises from unmeasured factors, or when there are large imbalances in baseline population characteristics. There are a variety of pharmacoepidemiological principles and biostatistical approaches to mitigate and control for potential bias. The same principles for designing valid observational studies using RWD, such as comparative effectiveness studies, can be applied to designing ECs.<sup>15</sup>

One helpful tool is the target trial framework, which helps researchers design an EC by characterizing and emulating a target RCT, which in the case of ECs is defined by the interventional trial, whether single arm or RCT.<sup>16</sup> The goal of the target trial framework is to enable valid causal inference through the design of

an EC that will result in exchangeability by selecting a cohort of patients with the same indication and stage of disease, a comparable distribution of baseline characteristics, and who will receive a similar level of care as the patients in the single-arm or hybrid trial.

Ideally, development teams should consider these concepts in the early stages of the program strategy, and the design of the single-arm trial or RCT and the EC should feed into each other and allow for cross-calibration. This strategy can facilitate greater comparability between inclusion/exclusion criteria, variable definitions, and outcome measures. Prespecification of the study design and analysis and proactive discussions of the study design and strategy with regulators are key components of the early design phase. In addition, researchers should publicly register study protocols to ensure transparency and avoid downstream concerns over cherry-picking the most supportive analysis and interpretations.

**Defining the research question.** Researchers must clearly articulate a well-formulated research question to be addressed by the EC, including defining precise endpoint(s) for safety and effectiveness and the timing of their assessment. While some general guidelines can be used, each specific clinical and regulatory context will drive the appropriateness of a strategy for use of ECs in the regulatory process.<sup>13</sup> Robust research questions can be developed through applying the concept of a target trial (which in the case of ECA is the single-arm or RCT to which the ECA will be compared).<sup>16</sup>

**Design of the target trial and defining the type of EC.** Most historic EC submissions have been included in a regulatory package alongside a single-arm trial of the investigational product. More recently, hybrid trials have been designed, in which a traditional RCT is constructed, and then the protocol is expanded to include additional external controls (usually based on RWD) that are then analyzed together with the trial controls or as a separate comparator to the active treatment arm(s). Such a hybrid RCT+EC design can enrich or augment an otherwise potentially underpowered RCT and can enable more robust interpretation of trial findings by providing additional context for comparisons. Enrollment of the EC in the hybrid RCT+EC may run concurrently with the trial, and may include some protocol-driven assessments that can increase reliability and complete ascertainment of variables in the EC. The small internal control arm of the RCT can be used in the traditional manner for direct comparisons with the active arm, and to enable assessment of the comparability of EC and trial patients. Use of a hybrid RCT+EC design might provide an opportunity to expand the regulatory use of ECs for nonrare or life-threatening indications for which trial enrollment is still challenging or very large sample-sizes are needed.

**Defining the timeframe for the EC.** As researchers design studies to promote valid evidence generation in ECAs, researchers must determine whether historic or concurrent controls are best suited to satisfying the design requirements for meaningful comparison of the EC and the trial (Figure 1). Historic data from previous trials, natural history studies, disease or product registries, or large

databases may be considered in cases in which standards of care are well defined and disease outcomes and management have remained stable. This often coincides with identification of a high unmet medical need and implied lack of progress in improvements in management and outcomes. In other cases, such as very active areas of medical product development, the standard of care may be changing so rapidly that historic data are no longer useful as a comparator, and data from a contemporaneous set of controls are needed for which the data are concurrent with the data from the clinical trial. It is also possible for an EC to comprise a mix of both historic and contemporaneous data.

### Building the study protocol requires considerable up-front planning

- **Eligibility criteria** – The core principle is to select patient data for ECs from the same population that gives rise to patients selected into the single-arm trial or RCT, and then apply the same eligibility criteria to select patient data for the EC (**Figure 3**). In RWD-constructed ECs, however, there are often challenges to precisely replicating eligibility criteria and tradeoffs need to be carefully considered. For example, limiting the EC population to the subset of patients in a RWD source with a full complement of trial eligibility criteria can lead to a small sample size and underpowered EC. Understanding the purpose of each inclusion and exclusion criterion and weighing the importance of those criteria should be undertaken to inform the EC, with good justification and documentation for the resulting EC eligibility criteria.
- **Standard of care** – Variability in standard of care by practitioners, care settings, and geographic location can result in between-group differences that impact the comparability or “exchangeability” of the EC and trial subjects. It is important to understand these factors and use that knowledge to inform the design of the EC, for example by including EC subjects from the same type of care settings, the same geographic locations, and possibly the same investigators as in the target trial. It may also be possible to adjust for some of these differences during the analysis stage, but only if sufficient attention was paid during the design phase to both understand and measure the important contributors.
- **Outcome selection and measurement** – One often challenging design element of particular concern in RWD-generated ECs is the ascertainment of the desired outcome measures. For all ECs, but especially direct hypothesis-testing ECAs, identical outcome measures would be ascertained with the same rigor at the same time-intervals as compared to the target trial. However, registrational clinical trials have evolved in many indications to frequently include specialized outcomes that are not typically measured in routine clinical practice, or if they are, are likely measured in a less standardized fashion, and at potentially disparate time intervals as compared to the highly controlled and monitored trial measures. Availability of measures in RWD may also correlate with timing of spontaneous medical visits when the patient is

**Figure 3 Key considerations for designing external control arms**



ill. These differences can result in difficulty identifying a suitable RWD resource for comparison to the trial, and to differential misclassification of outcomes, which if too large may invalidate the comparability of the EC and the trial. In general, ECs are better suited to comparisons based on objective clinical endpoints that are routinely measured in clinical practice.

- **Follow-up period** – In the single-arm trial or RCT, the follow-up period usually begins at time of randomization. For the EC, this can be challenging depending on the specific comparator being studied and the standard-of-care for the indication under study. In most cases, the follow-up period is usually set to begin at treatment initiation, assuming there is a specific sequence of therapy that is typically followed. In situations for which there is no available treatment, follow-up for the EC can be anchored to a specific time in the disease pathway. When leveraging existing datasets to construct an EC, it is important to avoid use of postbaseline data to select patients for the EC, and to avoid bias, patients missing postbaseline data should be considered lost to follow-up rather than excluded from the EC.<sup>17</sup> Another critical design feature of the EC is the appropriate definition for the baseline index date or time zero to avoid immortal time bias. Consideration of a new user design for a specified comparator drug or regimen can be helpful in mitigating this concern in some settings where such a comparison is of primary interest.

**Determining the most appropriate data source.** ECs can be constructed from many different types of data, including RWD or clinical trial data, and the data may be collected at the subject-level, or aggregate summary-level, and can be either historic or concurrent (Figure 1). RWD reflect the patient experience in routine clinical care, whereas data from previous RCTs were typically collected under highly specified and standardized protocols and procedures.

Many indication- and protocol-specific considerations enter the evaluation of the most appropriate data source to constitute each individual ECA and there is no one-size-fits-all solution. In all cases, the ECA subjects are selected to the extent possible in a manner designed to be comparable in baseline characteristics to the population enrolled in the clinical trial. Selection of the most appropriate type and source of data for construction of an EC involves careful consideration of numerous tradeoffs to arrive at a design that balances data quality and fitness-for-use with accessibility and cost of data acquisition. A crucial element for regulatory acceptability of the EC is the demonstration of comparability of data collection processes, variable definitions, and patient selection.

#### ***Statistical analysis plan and methods for adjustment***

As in most observational study designs, adequate control for confounding is critical for the EC to support valid causal inference. Core pharmaco-epidemiologic methods, including matching, standardization, inverse probability weighting, stratification, regression, g-estimation, or doubly robust methods,<sup>18</sup> are often used to control confounding in the analysis of an EC. Bayesian methods may also provide an efficient approach to design and analysis of EC, and the FDA has produced a guidance document for use of adaptive designs for trials of drugs and biologics<sup>19</sup> that can be used to inform such approaches.

Simulation is another strategy that can provide a flexible alternative analytical framework for analysis of ECs.<sup>20</sup> The clinical and regulatory context, specific research question, and available data inform the best strategy for analysis of each individual EC. In RWD-constructed ECs, the number of available covariates may be more limited than in the target trial, and common unmeasured confounders may be unavailable, such as diet and lifestyle, genetic factors, socioeconomic status, and other clinical features not collected in standard care settings, or not available or accessible in the particular data source being used. Sensitivity analyses are recommended for analysis of ECs to inform robustness of findings under varying assumptions.

#### ***Submission and review of evidence packages containing ECs***

Although there is a growing number of examples of regulatory use of ECs, clear guidance is lacking on when and how sponsors should engage with regulatory agencies when planning to undertake an EC for regulatory submission. An early engagement strategy seems prudent, and sponsors might consider the EC as an integral part of the overall development pathway rather than a separate regulatory conversation. At the same time, designing and implementing valid RWD-constructed ECs necessitates the involvement of RWD and RWE subject matter experts and many sponsor clinical development teams may lack this

expertise. Unfortunately, there also remain differences in requirements across regulatory agencies, which can complicate a sponsor's global regulatory strategy.<sup>21</sup> Future regulatory guidance on RWD-constructed ECs is anticipated, and both sponsors and regulators could benefit from more frequent interactions surrounding more granular design and submission requirements for regulatory use of ECs, including describing circumstances when ECs might be most applicable, method and timing for presentation of the rationale for the EC design and data source selection and curation, potential differences in requirements depending on the data source, the potential need for ancillary studies to validate real-world endpoints and measures used for inclusion and exclusion criteria.

### Conclusion

RWD-constructed ECs are an important use case for incorporation of RWE into regulatory decision making. Support for efficacy and safety can emerge from externally controlled trials, especially when:

- The natural history of a disease is well defined;
- The standard of care is well defined and not changing over time;
- There are high quality data available on key inclusion and exclusion criteria and clinically meaningful outcome measures;
- An external control population can be identified that is very similar to that of the treated group within the clinical trial;
- The appropriate analytic techniques are applied (e.g., propensity scores, inverse probability weighting);
- The results provide a compelling contrast to observed changes in outcomes of the trial (large treatment effect); and,
- The results are demonstrated via sensitivity analyses to be robust to variations in the analytic framework.

Because of the possibility of bias associated with use of ECs, and the well-established gold standard of the RCT for regulatory decisions, it is essential that the initial evaluation include feasibility of conduct of a traditional RCT for the indication and investigational product. In situations where ECAs are being developed, early regulatory input is recommended supported by a team with the appropriate scientific training in epidemiology and biostatistics to ensure a design, data, and methods that meet regulatory expectations. While their applicability for primary approvals is currently targeted toward certain development scenarios (e.g., rare indications with high unmet need), it is theoretically possible that use of ECs may broaden with greater regulatory experience gained in these early use cases. Careful evaluation of the clinical development context combined with vigilant epidemiological design of the EC are the most critical aspects to ensure comparability between the external controls and subjects in the active treatment arm of the target trial and to maximize the foundation for causal inference and consequent regulatory acceptability.

#### About the authors

**Debra Schaumberg, ScD, OD, MPH**, is vice president (epidemiology) and head of strategic & scientific affairs, real-world evidence at Evidera, a PPD business. She has more than 25 years of

experience designing and leading research investigations. In her current role, she conceptualizes and implements innovative RWE solutions across the drug development lifecycle that support regulatory approval and market access of medical treatments. Schaumberg received a doctor of science degree from the Harvard TH Chan School of Public Health, a master of public health degree from the Johns Hopkins Bloomberg School of Public Health, research fellowship at the Johns Hopkins University School of Medicine, and a doctor of optometry, summa cum laude, from the Illinois College of Optometry. She is the recipient of numerous awards, an elected Fellow of the American Academy of Optometry and the American College of Epidemiology, and adjunct professor of ophthalmology and visual sciences at the University of Utah School of Medicine. Schaumberg can be reached at [Debra.Schaumberg@evidera.com](mailto:Debra.Schaumberg@evidera.com)

**K. Jack Ishak, PhD**, is vice president (statistical methodology and strategy) at Evidera, a PPD business. Ishak is responsible for ensuring the application of best practices, developing novel methodologies, fostering flexible and integrated responses to client priorities, and promoting best-in-class capabilities and training internally. He specializes in predictive analyses to model disease processes that serve as the core of economic evaluations, treatment comparisons, and simulations of clinical trials. Ishak received an undergraduate degree in statistics from Concordia University and obtained a master's and doctoral degrees in biostatistics and epidemiology from McGill University. He can be reached at [Jack.Ishak@evidera.com](mailto:Jack.Ishak@evidera.com)

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