WHITE PAPER

# A framework for assessing the viability of an externally controlled arm for a single-arm trial

A KEY QUESTION

**Where does one begin to evaluate whether to incorporate an external control arm in their trial design or proceed with a traditional randomized clinical trial?**

KEYWORDS External Control Arm, Real-world Data, Oncology, Rare Disease

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An externally controlled trial is one in which the control group consists of patients who are not part of the trial and did not receive the investigational therapy (external control arm [ECA]). In such a trial, the endpoints of the trial patients (treated arm), are compared to the specified outcomes observed in the ECA. The main requirement of the ECA is that the patients are similar to the treated patients in the trial arm based on certain characteristics informed by the inclusion and exclusion criteria of the single-arm trial. The ECA can be a group of patients who are either from an earlier time (i.e., historical control) or from another setting during the same time-period (i.e., concurrent control). A distinct type of ECA is the synthetic control arm, which typically is created using historical patient-level data from multiple data sources that are standardized using appropriate statistical methods.

The United States Food and Drug Administration (FDA) has provided considerations for the design and analysis of an ECA, including "threats to the validity of trial results from potential bias" and also focusing "on the use of patient-level data from other clinical trials or real-world data (RWD) sources, such as registries, electronic health records (EHRs) and medical claims," with emphasis on data quality and accessibility.[1]

Despite the limitation of single-arm trials with respect to measuring efficacy and/or safety of the investigational therapy only in absolute terms because of the lack of placebo or a reference arm, the number of FDA approvals of therapies that are based on results from single-arm trials is on the rise. Accordingly, an increasing number of single-arm trials with an ECA are being proposed to support the application of new investigation therapies due largely to their practical advantages, including sample size and ethical considerations.[2] In the period between January 2019 and June 2021, as many as 116 of the 136 (85.3%) of the drugs approved by the FDA included real-world evidence (RWE) in the submission.[3]

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While randomized controlled trials (RCT) remain the standard for evaluating investigational therapies, RCTs might not be feasible in certain settings, such as:

- in oncology where the use of a placebo may not be ethical and the existing standard of care may not be effective, or
- in rare diseases where the number of eligible patients is typically small,[2] or
- when an uncontrolled, long-term extension of a randomized controlled trial is necessary because long-term use of a placebo or discontinuation of effective treatment is either unethical or not feasible.[4]

In this white paper, we describe the details of a checklist (ECA Viability Checklist) we developed to assess the critical aspects of a single-arm trial that involves RWD as an ECA when planning for a single-arm trial, which can be used to inform exploratory discussions with regulatory agencies. Our ECA Viability Checklist provides step-by-step guidance on the relevant questions to ask during the planning phase of the trial, with some recommendations on possible courses of action, based on the following:

- An FDA guidance document for the industry, namely, "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, Draft, February 2023"
- Data from trials submitted to the FDA where the FDA accepted evidence from RWD as an ECA for product approval or label expansion (Figure 1)[5-7]

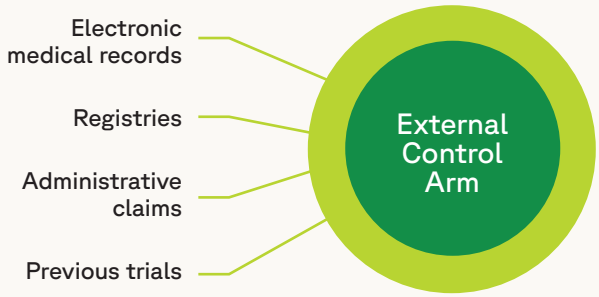
## Data sources for an ECA

Data sources to support an ECA may be patient-level data collected either:

- **Concurrently:** at the same time as the treated arm but in another setting (i.e., outside of the clinical trial)
- **Asynchronously:** at a different time than the treated arm (e.g., historical control)

Although ECAs can include data from the published literature, the focus of our white paper is on data from electronic medical records; registries; administrative, medical and pharmacy claims; and previous trials (Figure 1).[8] With respect to RWD, it is important to acknowledge that the availability of a data source containing patients with the disease of interest does not guarantee the availability of sufficient information on the relevant clinical characteristics. In this regard, we acknowledge the value of the SURF screening tool, which is based on answers to six specific questions to help sponsors assess the feasibility of using an RWD source for an ECA.[9]

**Figure 1:** Data sources to support an external control arm



## The ECA viability checklist

Below, we walk through our 10 questions that make up our ECA Viability Checklist to assess the viability of an ECA that uses RWD to support a single-arm trial (Figure 2). Ideally, all responses to our checklist questions would be "Yes" to be most confident in regulatory acceptance of the proposed ECA. Any "No" response should include adequate rationale/reason(s). In these situations, with particular focus on the FDA, we provide some recommendations on possible progress in terms of the viability of a proposed ECA.

### Q1. Is the disease rare and/or is it unethical/not feasible to conduct a randomized trial?

**Yes:** Such settings are generally favorable to an ECA, especially for a life-threatening and/or severely debilitating disease with unmet medical need. A proactive initiation of a disease natural history study is recommended where there is a gap in knowledge of the disease.

**No:** There still may be reasonable grounds for an ECA if the disease is rare, even if it may be feasible to conduct a randomized trial. Such circumstances include therapies with evidence of efficacy from early-Phase clinical studies (i.e., Phase I and/or II), supported by the literature (i.e., natural history of the disease) that indicates serious unmet need, especially for a life-threatening or severely debilitating disease.

### Q2. Is there no alternative therapy for comparison with the therapy of interest?

**Yes:** Situations where there is no alternative therapy for comparison are generally favorable candidates for an ECA, especially if it may not be feasible to conduct a placebo-controlled trial.

**No:** Explore the possibility of using data from a past trial involving the therapy for the comparison. The main factors to consider include: possible impact of differences in the assessments of the outcomes of interest, the time periods, the inclusion/exclusion criteria, administration of the two therapies and the patterns of care. Where such data are either not available or they are not sufficiently suitable to serve as the ECA, a literature review may be conducted on the current management of the disease. Depending on the findings, the feasibility of initiating a disease natural history study that involves assessment of the effectiveness of the current treatments in routine practice, which may serve as the ECA, may be explored.

### Q3. Is disease progression clinically predictable such that spontaneous change in the absence of an intervention is not a feature of its course?

**Yes:** Such settings are favorable candidates for regulatory agency approval (i.e., FDA), with disease natural history studies generally considered as suitable for the ECA.

**No:** The effect of the therapy of interest on the target condition from other influences, "such as spontaneous change in the course of the disease, placebo effect or biased observation"[1] will need to be described. This aspect should be included in prior discussions with the regulatory agency.

### Q4: Can the estimand framework,[1,10] as described in Figure 2, be used to quantify the treatment effect consistently?

**Yes:** This will likely enhance the suitability of the proposed ECA for the trial.

**No:** The problematic attributes of the estimand framework (i.e., treatment, population, outcome/endpoint of interest, handling of intercurrent events and the population-level statistical summary to be used to compare treatment effects) will need to be identified and the feasibility of making the necessary changes explored, which will facilitate its suitability and adoption.

### Q5: Is the outcome of interest related to an objective event and/or does it require immediate medical attention?

**Yes:** This will likely enhance the suitability of the proposed ECA for the trial, and it is even more suitable where the relevant prognostic factors for the outcome are known.

**No:** It is vital that the outcome is objective, especially in the sense that it can be reliably measured consistently. For this reason, feasibility of utilizing an alternative outcome/endpoint that will satisfy this requirement should be explored, including suitable surrogate(s). This aspect should be included in prior discussions with the regulatory agency.

### Q6: Is there suitable data on the disease population with information on standard of care/alternative treatment(s) and other patient-level data?

**Yes:** This will likely enhance the suitability of the proposed ECA for the trial.

**No:** It may be useful to initiate a suitable disease natural history study that includes standard of care ahead of the proposed ECA trial.

### Q7: Can data be obtained on the key/necessary prognostic factors of the outcome of interest, including the patient characteristics?

**Yes:** This will likely enhance the suitability of the proposed ECA for the trial.

**No:** Since prognostic factors are associated with the clinical outcome in patients on standard of care in the absence of therapy, such data are vital for an ECA to be considered as suitable. For this reason, the feasibility of initiating a suitable disease natural history study to obtain data on such relevant prognostic variables may have to be considered.

### Q8: Can a patient population be obtained to serve as control that is similar to the trial population in terms of the prognostic factors and patient characteristics?

**Yes:** This will likely enhance the estimation of the counterfactual and thus, the suitability of the proposed ECA for the trial.

**No:** One of the possible alternatives is to conduct a comprehensive literature review for suitable evidence, which may serve as the ECA. In the absence of such evidence, the feasibility of initiating a suitable disease natural history study for the purpose may have to be considered. These two options should be among the main points for prior discussions with the regulatory agency.

### Q9: Is the size of the anticipated treatment effect of interest large enough to be able to distinguish the effect from other sources of influence on the outcome (i.e., bias and confounding)?

**Yes:** This will likely enhance the suitability of the proposed ECA for the trial.

**No:** This is a major point for prior discussion with the regulatory agency, having already conducted a literature review to identify the possible range of suitable effect sizes. Indeed, the Agency recommends that a statistical analysis plan, along with a protocol, be submitted to its "relevant review division before initiation of patient enrollment" in such a clinical trial.[1]

### Q10: Is the anticipated treatment effect of interest consistently measured in routine management of the patient population, or can adequate surrogate(s) of the measure be obtained?

**Yes:** This will likely enhance the suitability of the proposed ECA for the trial.

**No:** This may call for the initiation of a suitable observational (i.e., non-interventional) study involving sites that are either capable of measuring the treatment effect of interest or its surrogate(s) consistently (i.e., prospective chart review) or already contain such records (retrospective chart review). The other alternative may be to identify appropriate secondary databases from which to assess the feasibility of obtaining a suitable ECA candidate for discussions with the regulatory agency.

**Figure 2:** External control arm viability checklist

| Order | Checklist item | If checklist item is not upheld |
|---|---|---|
| 1. | The disease is rare and/or it is unethical/not feasible to conduct a randomized trial.[a,b] | An ECA trial may still be feasible, especially for life-threatening or severely debilitating diseases such as for therapies with positive results from clinical studies, supported by the literature that indicate serious unmet need. |
| 2. | There is no therapy for comparison. | Hold discussions with the regulatory agency prior to implementing. Explore the possibility of using data from either a past trial involving a suitable therapy for the comparison, considering the possible impact of any relevant differences in the assessments of the outcomes of interest or a literature review on the current management of the disease. Alternatively, propose to initiate a disease natural history study that involves assessment of the effectiveness of the current treatments in routine practice to serve as the ECA. |
| 3. | Progression of the disease is clinically considered as predictable, and spontaneous change in the absence of an intervention is not a feature of the course of the disease. | Hold discussions with the regulatory agency about the intended method for distinguishing the effect of the therapy on the target condition from other influences before implementing the ECA. |
| 4. | The estimand framework[1,10] can be used to quantify the treatment effect consistently.[c] | Hold discussions with the regulatory agency around the problematic aspects of the framework and the intended solutions before implementing the ECA. |
| 5. | The outcome of interest is related to an objective event and/or requires immediate medical attention.[d,e] | Hold discussions with the regulatory agency around the intended alternative outcome that will satisfy this requirement, including suitable surrogate(s), before implementing the ECA. |
| 6 | There is suitable data on the disease population with information on standard of care and other patient-level data.[d] | Hold discussions with the regulatory agency about a proposal for a disease natural history study, before implementing the ECA. |
| 7. | Data can be obtained on the key/necessary prognostic factors and patient characteristics. | Initiate a suitable disease natural history study to obtain the relevant data. |
| 8. | A patient population can be obtained to serve as control that is similar to the trial population in terms of the prognostic factors and patient characteristics. | Hold discussions with the regulatory agency before implementing an ECA about a comprehensive literature review and/or a proposal for a disease natural history study. |
| 9. | The size of the anticipated treatment effect of interest is large enough to be able to distinguish the effect from other sources of influence on the outcome (i.e., bias). | Hold discussions with the regulatory agency before implementing an ECA after having already conducted a literature review on the disease natural history, including a standard of care that indicates significant unmet medical need and before implementing an ECA. |
| 10. | The anticipated treatment effect of interest is consistently measured in routine management of the patient population or adequate surrogate(s) of the measure can be obtained. | Hold discussions with the regulatory agency about conducting a chart review involving sites that are either capable of measuring the treatment effect of interest or its surrogate(s) consistently, before implementing an ECA. |

ECA, external control arm

a. Importance about "owning the disease" - due to concern about transparency regarding data collection and analysis, the FDA guidance on use of RWD states: *"Sponsors should engage with FDA in the early stages of designing a non-interventional study intended to support a marketing application. For example, sponsors can request a Type C meeting with the appropriate review division to discuss Agency expectations for the design and conduct of their studies. Sponsors should provide draft versions of their proposed protocol and statistical analysis plan for Agency review and comment, prior to finalizing these documents and before conducting the study analyses."* (FDA Guidance, Draft, February 2023)

b. Life-threatening and severely debilitating diseases with unmet medical needs are particularly suitable. (FDA Guidance, Draft, February 2023)

c. The estimand framework is a structured approach used in clinical trials to clearly define the treatment effect of interest by ensuring alignment between the trial objective, trial design, endpoint(s) and analysis. It defines the estimand based on five attributes: treatment, population, outcome/endpoint of interest, handling of intercurrent events (i.e., events that occur after the start of the trial which may affect the presence and/or interpretability of observed values) and the population-level statistical summary to be used to compare treatment effects.[10]

d. More suitable where the relevant prognostic factors for the outcome are known. Where "the natural history of a disease is well-defined and the disease is known not to improve in the absence of an intervention or with available therapies, historical information can potentially serve as the control group." (FDA Guidance, Draft, February 2023)

e. Strongly recommend initiation of disease natural history study in response where there is a gap in knowledge of the disease (prospective versus retrospective such as chart review/literature review/EHRs, etc.) (FDA Guidance, Draft, February 2023)

## ECA examples

We evaluated our ECA Viability Checklist against five trials that were supported with an ECA where the product was successfully approved by the FDA. We obtained affirmative responses to all 10 ECA Viability Checklist questions/items for four of the trials and at least five affirmative responses without qualification for the fifth trial (Figure 3).

**Figure 3:** Evaluation of five clinical trials against our ECA viability checklist

| FDA approved trials with external control arms | | | | | |
|---|---|---|---|---|---|
| Checklist item | **NCT01209286**[11]<br><br>**Oncology:** Blincyto® (blinatumomab) for the treatment of acute lymphoblastic leukemia (ALL).<br><br>**ECA:** Historical cohort of adult patients with relapsed/refractory ALL on standard therapy. | **NCT02601950**[12,13]<br><br>**Oncology:** Tazverik® for patients with histologically confirmed, metastatic or locally advanced epithelioid sarcoma (ES) that are not eligible for complete resection.<br><br>**ECA:** Natural history study of patients with ES on standard therapy who had not received Tazverik to demonstrate unmet need. | **NCT02508532**[14]<br><br>**Oncology:** Avapritinib® for the treatment of patients with advanced cases of gastrointestinal stromal tumor (GIST) that have a certain genetic mutation.<br><br>**ECA:** Natural history study (retrospective analysis) of patients with unresectable/ metastatic platelet-derived growth factor receptor A (PDGFRA) D842V-mutant GIST. | **NCT01163149**[15]<br><br>**Rheumatology:** Strensiq® for the treatment of perinatal, infantile and juvenile onset hypophosphatasia.<br><br>**ECA:** Natural history study of patients with perinatal and infantile hypophosphatasia. | **NCT00382109/ NCT03513328/ NCT00566696**[16]<br><br>**Hematology:** Tepadina® for graft rejection prior to hematopoietic stem-cell transplantation in children with Class 3 beta-thalassemia.<br><br>**ECA:** Historical cohort of patients undergoing bone marrow transplantation from a human leukocyte antigen (HLA)-identical sibling donor for thalassemia and microdrepanocytosis. |
| **1. The disease is rare and/or it is unethical/ not feasible to conduct a randomized trial.** | Yes<br><br>Accounts for less than half of 1% of all cancers in the U.S. age-standardized rates ranging from approximately one to two per 100,000 across various geographies. | Yes<br><br>Incidence of about 0.1 cases per million in the U.S. | Yes<br><br>Only 5% to 10% of GISTs have a PDGFRA mutation. Avapritinib was granted an orphan drug designation. | Yes<br><br>A total of about 3,200 cases in the U.S. | Yes<br><br>Considered rare despite more than 100,000 affected children being born each year. |
| **2. There is no therapy for comparison.** | Yes | Yes | Yes | Yes | Yes<br><br>Bone marrow transplantation is the only effective intervention. Those who undergo a second allogeneic HSCT have a significant risk of graft failure, transplant-related mortality and lower thalassemia-free survival. There is an unmet need. |

**Figure 3:** Data sources to support an external control arm (cont'd)

| | | | | | |
|---|---|---|---|---|---|
| **3. Progression of the disease is clinically considered as predictable, and spontaneous change in the absence of an intervention is not a feature of the course of the disease.** | Yes | Yes | Yes | Yes | Yes |
| **4. The estimand framework can be used to quantify the treatment effect consistently.** | Yes | Yes | Yes | Yes | Yes<br>Despite the unfavorable summary conclusion of the statistical review, namely—*"This reviewer recommends that claims based on historical controls or a literature meta-analysis should not be allowed since the pivotal trial did not prospectively plan for these comparisons".* |
| **5. The outcome of interest is related to an objective event and/or requires immediate medical attention.** | Yes<br>Complete remission and overall survival. | Yes<br>Overall response rate, progression-free survival and overall survival. | Yes<br>Overall survival and progression-free survival. | Yes<br>Overall survival and invasive ventilator-free survival. | Yes<br>Incidence of graft rejection, overall survival, thalassemia-free survival and transplant-related mortality. |
| **6. There is at least one instance of suitable data on the disease population with information on standard of care and other patient-level data.** | Yes | Yes | Yes | Yes | Yes<br>Despite unfavorable statistical review—namely, *"Some differences in study characteristics, patient populations and follow up times make it difficult to make statistical inferences in comparison to the corresponding efficacy results of the trial".* |

**Figure 3:** Data sources to support an external control arm (cont'd)

| | | | | | |
|---|---|---|---|---|---|
| **7. Data can be obtained on the key/necessary prognostic factors and patient characteristics.** | Yes | Yes | Yes | Yes | Yes<br>Despite unfavorable statistical review—namely, *"While source data for the primary efficacy endpoint, incidence of graft rejection, was verified, some secondary endpoint data was not validated".* |
| **8. A patient population can be obtained to serve as control that is similar to the trial population in terms of the prognostic factors and patient characteristics.** | Yes | Yes | Yes | Yes | Yes<br>Despite mixed statistical review—namely, *"The trial has a retrospective study design with historical, unmatched controls. Thus, there is no evidence that the study's treatment arms are comparable".* |
| **9. The size of the anticipated treatment effect of interest is large enough to be able to distinguish the effect from other sources of influence on the outcome (i.e., bias).** | Yes | Yes | Yes | Yes | Yes |
| **10. The anticipated treatment effect of interest is consistently measured in routine management of the patient population or adequate surrogate(s) of the measure can be obtained.** | Yes | Yes | Yes | Yes | Yes<br>Despite mixed statistical review—namely, *"The timing of follow up differs across studies. Therefore, meta-analysis results are not supportive of the results from protocol...".* |

## Our recommendations

**When selecting an ECA try to:**

**1.** Minimize operational bias from the various possible sources such as data collection, measurement of key variables and outcomes and data analysis by adopting the most appropriate strategies (e.g., the use of standardized processes for data handling, assessments and analysis).

**2.** Ensure that the external population is similar to the treated arm in the trial population in terms of the relevant prognostic factors and patient characteristics, whilst flexibly adopting the following Pocock's criteria that are applicable:[17,18]

- ECA patients received a precisely defined standard of care
- ECA eligibility criteria and methods of treatment evaluation is the same for the treated arm
- Distributions of the prognostic factors and important patient characteristics in the ECA are comparable at baseline (i.e., at the start of follow-up)
- There are no other important indications or differences between the ECA and treated arm capable of affecting the study results
- Preferably, the comparative analysis is conducted with the same contract research organization or investigator(s)

**Additionally, the following five attributes of the estimand framework should inform the study design and analysis to facilitate comparability between the treated arm and the ECA:**[1,10]

- Treatment of interest
- Target population
- Intercurrent events
- Endpoint of interest
- Population level summary of the treatment effect

**A focus on comparability should be made in the following areas:**[1]

- Appropriate methodology for comparing the endpoints/outcomes between the ECA and single-arm trial populations that adequately accounts for the influence of the prognostic factors at baseline
- Changes/variations (over time/between regions) in the following: clinical care, standard of care, access to care, healthcare system, diagnosis, treatment and differences in follow-up time
- Designation of index date for start of follow-up in situations in which no treatment is the treatment strategy for the ECA (i.e., immortal time bias)[19]

**With respect to analysis, we recommend the following:**[1]

- Use an analytic method that identifies and manages sources of confounding and bias, with provisions to account for differences in prognostic factors and important patient characteristics between the treated arm and the ECA
- Avoid assumptions in the analysis which may be difficult to substantiate because such may impair the interpretability of the results (e.g., time-dependent treatment effect) and conduct appropriate sensitivity analyses of any such assumptions
- Ensure the estimand is not changed. Propensity scores are a common method used to evaluate comparability, either for matching or as weights. However, each approach has its limitations, and the focus should be to ensure the estimand is not changed

## Our conclusions

Evaluation against our ECA Viability Checklist will enable those responsible for assessing the viability of an ECA to arrive at an informed decision on whether and/or how to proceed with an ECA. Next steps may include engaging the regulatory agencies in explorative discussions, exploring an alternative trial design (e.g., randomized controlled trial) or assessing the feasibility of initiating a disease natural history study.

In discussions about an ECA, the regulatory agency would expect sponsors to describe or justify the following areas, for which our ECA Viability Checklist can be particularly useful:

- The appropriateness of the proposed study design
- The proposed data sources for the ECA and suitability for the desired purpose
- The intended statistical analyses
- The plans for addressing the regulatory agency's expectations for the submission of such data[1]

Our ECA Viability Checklist is based on the expertise and experience of epidemiologists and RWE scientists in Market Access Consulting & HEOR at Fortrea Inc., our interpretation of the FDA guidance and FDA approvals regarding submissions with RWD supporting an ECA. Our team is uniquely equipped with the necessary expertise, experience and operational capabilities to provide services in both the planning and conduct of such studies, including assessment of an ECA, recommendations for the type of RWD suitable for the ECA and facilitation of engagement with regulatory agencies from our RWE scientists and regulatory strategists.

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