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

Victor A. Kiri, MPH, PhD,[1] Kathryn M. Plante, MS[2]

[1]Fortrea Market Access Consulting & HEOR, Maidenhead, United Kingdom
[2]Fortrea Market Access Consulting & HEOR, Durham, North Carolina, United States

Abstract

- **OBJECTIVES:** A single-arm trial with an external control arm (ECA) is one in which the patients in the control group do not participate in the trial. The number of approved ECA trials is on the increase, due largely to their practical advantages, including sample size and ethical considerations. Given this, we developed a framework to make initial assessments on the viability of an ECA in meeting regulatory requirements (i.e., ECA checklist). The purpose of the ECA checklist is to inform exploratory discussions with regulatory agencies, who would expect study sponsors to establish the appropriateness of the proposed design, data sources, and statistical analyses.
- **METHODS:** The ECA checklist is based on relevant United States Food and Drug Administration guidance documents and the literature on over 40 accepted ECA trials across different therapeutic areas. It is structured on the critical aspects of design and analytical considerations on the use of real-word data and past trials, presented as 10 thematic questions with recommendations on possible solutions to issues arising from each theme. We evaluated the checklist against 5 ECA trials.
- **RESULTS:** Ideally, all thematic checklist responses would be affirmative to be most confident of regulatory acceptance of the ECA; non-affirmative responses would require adequate rationale, guided by the associated recommendations for progression. In our evaluation against 5 approved ECA trials, we obtained affirmative responses for at least 8 themes.
- **CONCLUSIONS:** Use of the ECA checklist will enable decision-makers to make an initial viability assessment of the ECA and make an informed decision on required next steps to help ensure acceptance of the ECA design. Such steps may include an assessment of the feasibility of initiating a disease natural history study, an appointment with the relevant regulatory agency for explorative discussions, or an exploration of alternative study designs, such as a randomized controlled trial.

Background

- 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 study outcomes of the trial patients (treated arm) are compared to the outcomes in the ECA
- The main requirement of the ECA is that patients are similar to the patients in the trial arm based on certain characteristics; thus, 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 period (i.e., concurrent control)
- The United States Food and Drug Administration (FDA) has recommended certain areas for consideration in the design and analysis of the ECA, including "threats to the validity of the results from potential bias"[1]
- The FDA also "focuses on the use of patient-level data from either other clinical trials or real-world data sources, such as registries, electronic health records and medical claims," with emphasis on data quality and accessibility[1]
- An increasing number of single-arm trials with an ECA are being proposed to support the application of new 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 in the submission[2]

Objective

- To describe the details of a checklist we developed to assess the critical aspects of single-arm trials that involve real-world data as an ECA, which can be used to inform exploratory discussions with regulatory agencies

Methods

- The checklist was based on the FDA Guidance (*Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products, Draft, February 2023*) and evidence from the literature on applications where the FDA has accepted evidence from RWD as ECAs for product approval or label expansion[3-5] **(Figure 1)**
- It provides step-by-step guidance on the relevant questions to ask when planning for an ECA in a single-arm trial
- Ideally, all responses would be "Yes" to be most confident in regulatory authority acceptance of the proposed ECA
- Any "No" response should include adequate rationale/reason(s) with the checklist providing some recommendations for possible progression in such circumstances
- We evaluated the checklist against 5 successful trials with an ECA:
  - **NCT01209286:** An Open Label, Multicenter, Exploratory Phase II Study to Evaluate the Efficacy, Safety, and Tolerability of the BiTE® Antibody Blinatumomab in Adult Patients With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia
  - **NCT02601950:** A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects With INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma
  - **NCT02508532:** A Phase 1 Study of BLU-285 in Patients With Gastrointestinal Stromal Tumors (GIST) and Other Relapsed and Refractory Solid Tumors
  - **NCT01163149:** A Randomized, Open-Label, Multicenter, Multinational, Dose-Ranging, Concurrent Control Study of the Safety, Efficacy, Pharmacokinetic of ENB-0040 (Human Recombinant Tissue Nonspecific Alkaline Phosphatase Fusion Protein) in Adolescents and Adults With Hypophosphatasia
  - **NCT00382109/NCT03513328/NCT00566696:** Series of trials including (1) A Randomized Trial of Sirolimus-Based Graft Versus Host Disease Prophylaxis After Hematopoietic Stem Cell Transplantation in Relapsed Acute Lymphoblastic Leukemia; (2) A Reduced Intensity Conditioning Regimen With CD3-Depleted Hematopoietic Stem Cells to Improve Survival for Patients With Hematologic Malignancies Undergoing Haploidentical Stem Cell Transplantation; (3) PEDS024, Phase I/II Feasibility Study of Busulfan Fludarabine and Thiotepa Conditioning Regimen for Allogeneic Hematopoietic Stem-Cell Transplantation for Children With Non-Malignant Disorders

Results

- All 5 trials satisfied the 10 themes in our checklist **(Figure 2)**
- The Tepadina trial (NCT00382109/NCT03513328/NCT00566696) was successful despite mixed and unfavorable statistical review **(Figure 2)**

Figure 1: A Checklist for the Use of an External Control Arm in a Trial

Order	Theme/Question	Response
1	The disease is rare and/or it is unethical/not feasible to conduct a randomized trial [*No: An ECA trial may be feasible, especially for life-threatening and severely debilitating diseases- such as for therapies with positive results from clinical studies, supported by the literature that indicates serious unmet needs*]	❑ Yes[a,b] ❑ No
2	There is no therapy for comparison [*No: Such a setting is generally favourable for an ECA trial, especially if it may not be feasible to conduct placebo-controlled trial*]	❑ Yes ❑ No
3	Progression of the disease is clinically considered as predictable and spontaneous change in the absence of an intervention is not a feature of its course [*No: Prior discussion with the FDA, the intended method for distinguishing the effect of the therapy on the target condition from other influences*]	❑ Yes ❑ No
4	The estimand[c] framework can be used to quantify the treatment effect consistently [*No: Prior discussion with the FDA, the problematic aspects of the framework and the intended solutions*]	❑ Yes ❑ No
5	The outcome of interest is related to an objective event and/or requires immediate medical attention [No: *Prior discussion with the FDA, the intended alternative outcome that will satisfy this requirement, including suitable surrogate(s)*]	❑ Yes[d,e] ❑ No
6	There is at least one suitable database on the disease population with information on standard of care and other patient-level data [*No: Prior discussion with the FDA, a proposal for a disease natural history study*]	❑ Yes[d] ❑ No
7	We can obtain data on the key/necessary prognostic factors and patient characteristics [*No: Initiate a suitable disease natural history study to obtain the relevant data*]	❑ Yes ❑ No
8	We can obtain patient population to serve as control that is similar to the trial population in terms of the prognostic factors and patient characteristics [No: Prior discussion with the FDA: (1) conduct a comprehensive literature review and/or (2) *a proposal for a disease natural history study*]	❑ Yes ❑ No
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 (ie, bias) [*No: A major point for prior discussion with the FDA, having already conducted a literature review*]	❑ Yes ❑ No
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 [*No: Prior discussion with the FDA for a chart review involving sites that are either capable of measuring the treatment effect of interest or its surrogate(s) consistently*]	❑ Yes ❑ No

ECA, external control arm

a. Important 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 provides detailed description of the treatment effect for quantification, and consists of 5 attributes: treatment, population, outcome 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 of interest.
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)3

Figure 2: Evaluation of 5 Clinical Trials Against Our Checklist

Checklist Theme	FDA Approved Trials with External Control Arms				
	NCT01209286 **Oncology:** Blincyto® (blinatumomab) for the treatment of acute lymphoblastic leukemia **ECA**: Historical cohort of adult patients with relapsed/refractory acute lymphoblastic leukemia on standard therapy	**NCT02601950** **Oncology:** Tazverik® for patients with histologically confirmed, metastatic or locally advanced epithelioid sarcoma (ES) that are not eligible for complete resection. **ECA**: Natural history of patients with ES on standard therapy who had not received Tazverik to demonstrate unmet needs	**NCT02508532** **Oncology:** Avapritinib® for the treatment of patients with advanced cases of gastrointestinal stromal tumor (GIST) that have a certain genetic mutation. **ECA**: Natural history (retrospective analysis) of patients with unresectable/metastatic platelet-derived growth factor receptor A (PDGFRA) D842V-mutant GIST	**NCT01163149** **Rheumatology:** Strensiq® for the treatment of perinatal, infantile and juveniles with onset hypophosphatasia. **ECA**: Natural history (retrospective analysis) of patients with perinatal and infantile hypophosphatasia.	**NCT00382109/NCT03513328 NCT00566696** **Hematology:** Tepadina® for graft rejection prior to hematopoietic stem-cell transplantation (HSCT) in children with Class 3 beta-thalassemia. **ECA**: Historical cohort of patients undergoing bone marrow transplantation from a human leukocyte antigen (HLA)-identical sibling donor for thalassemia and microdrepanocytosis
Rare disease	Yes Accounts for less than half of 1% of all cancers in the US Age-standardized rates ranging from approximately 1 to 2 per 100,000 across various geographies	Yes Incidence of about 0.1 cases per million in the US	Yes Only 5% to 10% of GISTs have a PDGFRA mutation. Avapritinib was granted an orphan drug designation	Yes A total of about 3,200 cases in the US	Yes Considered as rare despite more than 100,000 affected children being born each year
No effective treatment	Yes	Yes	Yes	Yes	Yes Bone marrow transplantation being 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 unmet need
Predictable progression/not spontaneous	Yes	Yes	Yes	Yes	Yes
The estimand framework	Yes	Yes	Yes	Yes	Yes 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*"
Objective outcome(s)	Yes Complete remission and overall survival	Yes Overall response rate, progression-free survival and overall survival	Yes Overall survival and progression-free survival	Yes Overall survival and invasive ventilator-free survival	Yes Incidence of graft rejection, overall survival, thalassemia-free survival, and transplant-related mortality
Suitable data on standard of care	Yes	Yes	Yes	Yes	Yes 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*"
Suitable data with the required prognostic factors	Yes	Yes	Yes	Yes	Yes 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*"
Control patients comparable with the trial patients	Yes	Yes	Yes	Yes	Yes 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*"
Treatment effect is clinically large enough despite the risk of bias	Yes	Yes	Yes	Yes	Yes
Treatment effect is consistently measured in routine practice	Yes	Yes	Yes	Yes	Yes 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…*"

Conclusions

- Evaluation against the checklist will enable those responsible for assessing the feasibility of an ECA to arrive at an informed decision on the necessary next step(s)
- Such steps may include assessing the feasibility of initiating a disease natural history study, engaging regulatory agencies in formal explorative discussions, or exploring an alternative study design, such as a randomized controlled trial
- In discussions about an ECA, the regulatory agency would expect sponsors to describe or justify the following areas, for which the checklist can be particularly useful:
  - Appropriateness of the proposed study design
  - Proposed data sources for the ECA and suitability for the desired purpose
  - Intended statistical analyses
  - Plans for addressing the expectations for the submission of such data[1]
- The checklist is a useful resource for discussions with regulatory authorities

References:
1. FDA Guidance for Industry: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. https://www.fda.gov/regulatory-information/search-fda-guidance.
2. Purpura CA, Garry EM, Honig N, Case A, Rassen JA. The Role of Real-World Evidence in FDA-Approved New Drug and Biologics License Applications, *Clin Pharmacol Ther.* 2022;111:135-144.
3. Cucherat M, Laporte S, Delaitre O, et al. From single-arm studies to externally controlled studies. Methodological considerations and guidelines. *Therapies*, 2020, 75 (1), pp. 21-27.
4. Thorlund K, Dron L, Park JJH, Mills EJ. Synthetic and External Controls in Clinical Trials - A Primer for Researchers. *Clin Epidemiol.* 2020 May 8;12:457-467.
5. Jahanshahi M, Gregg K, Davis G, et al. The Use of External Controls in FDA Regulatory Decision Making. *Ther Innov Regul Sci.* 2021 Sep;55(5):1019-1035.

ISPOR Europe 2024