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Strategic considerations when planning an externally controlled single-arm trial

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To support drug development sponsors with their externally controlled clinical trials, real-world evidence (RWE) scientists within Fortrea Consulting, have interpreted the U.S. Food & Drug Administration's (FDA's) guidance document, "Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products." This white paper outlines the critical aspects of single-arm trials that use real-world data (RWD) to support an external control arm (ECA). It highlights some of the design and analytical challenges that warrant careful consideration.

Background

The 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*." 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 (EHR) and medical claims,"[1] with emphasis on data quality and accessibility.

Despite the increasing number of FDA approvals of pharmaceutical therapies based on results from single-arm trials, randomized controlled trials (RCTs) remain the gold standard for the evaluation of investigational therapies. Therapies with "*greater risks may require a greater magnitude of benefit to support their approval*"[2] and RCTs might not be feasible in certain settings, such as in oncology or rare diseases, where the use of a placebo may not be ethical, the existing standard of care may not be effective, or where the number of eligible patients is likely very small. An ECA in a long-term extension of an RCT may be necessary due to the challenge of using a placebo either because it may be unethical or not feasible to do so.[3]

A single-arm trial consists of patients who are enrolled and followed up prospectively as they receive the investigational therapy. Such trials enable assessment of the effectiveness and safety in absolute terms (i.e., not directly compared to either a placebo or a reference therapy). For this reason, such trials do not directly provide comparative evidence of the benefit of the investigational therapy. Despite this drawback, an increasing number of single-arm trials are being proposed to support the application of new therapies for the reasons previously described.[4]

A systematic review of non-randomized trials that involved ECAs, which were submitted as the main evidence-base in applications for regulatory approval across several indications between 2005 and 2017, identified 43 applications (34 to the EMA, 41 to the FDA), from which the FDA approved 98% of submissions (56% as accelerated approvals and most requiring post-approval confirmatory RCTs) and the EMA approved 79% of submissions (25% being conditional on completion of a post-approval RCT or additional non-randomized trials).[5] The review also reported an increasing pattern of submissions between 2005 to 2011 and 2012 to 2017.

An externally controlled trial is one in which the control group consists of patients who do not receive the investigational therapy. As such, the endpoints in participants receiving the investigational therapy are compared to endpoints in patients external to the trial (i.e., not enrolled in the trial) who did not receive the therapy. Patients in the ECA must be similar to the enrolled patients based on certain characteristics. Thus, the ECA can be a group of patients who are either from an earlier time (i.e., a historical control) or during the same period of time (i.e., a concurrent control).

The FDA has a long history of using RWE to monitor and evaluate the safety of approved therapies in the post-marketing environment, where it uses data from EHRs, for example, with the Sentinel System.[6] Real-world data can be used as an ECA for interpreting the long-term safety and efficacy results from single-arm trials.[1,7] The use of historical RWD, as a benchmark, can be particularly useful for characterizing the natural history of the disease, including treatment patterns and outcomes for a disease that is not only rare but also has insufficient data about its natural history (e.g., severe unmet need, scarcity of available patients).[5,8,9] This is particularly useful when there have been no noticeable shifts in the standard of care, medical practice, patient management or patient characteristics as the historical RWD provides insight into how the disease progresses over time under standard care.[10,11] This is different from that of an ECA that involves concurrent RWD to serve as the control arm of the trial.

In common with epidemiological literature, the FDA defines disease natural history as the "*course a disease takes in the absence of intervention in individuals with the disease, from the disease's onset until either the disease's resolution or the individual's death*".[12] In this context, a natural history study is a "*preplanned observational study intended to track the course of the disease and its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes.*"[13] By design, such studies will not only include patients on the current standard of care, but also those on any emergent care, which may alter some manifestations of the disease. In this regard, the FDA has identified disease registries as highly useful resources for acquiring data for such studies.

Design considerations

We concur with the FDA that the potential for bias in externally controlled trials can be best addressed in the design phase because "*well-chosen design elements increase confidence in the interpretability of the results when appropriate analytical methods are applied to estimate treatment effects.*"[1] The FDA recommends the following as the main areas of relevance to the design, which ideally should be determined before initiating the trial: (1) selection of an appropriate patient-level ECA, (2) analytic approach, (3) patient eligibility criteria, (4) appropriate definitions for both exposure and endpoints of interest and (5) procedures for minimizing missing data and sources of bias.

Other key recommendations involve the:

- **The estimand framework**
  The FDA recommends the use of the "estimand" framework for the study design.[14] The estimand is described as a precise definition of the treatment effect to reflect the clinical question posed by the study objective. Its framework consists of the following five attributes: (1) population, (2) treatment of interest and comparator, (3) endpoints of interest, (4) study population-level summary of the endpoints of interest and most importantly, (5) handling of the intercurrent events—namely, those events that occur during the study follow-up, which can affect the interpretability of the observed values (e.g., emergency medication or treatment discontinuation due to adverse events).

  A central aspect of the estimand framework is its focus on possible intercurrent events along with strategies for minimizing their impact. Such strategies include pre-specified plans for identifying the sources of bias and for handling important confounding factors, despite the difficulties associated with the process of identifying confounding factors in RWD. For example, data on some key confounding factors may be either incomplete or missing on some patients or measured differently in the ECA.[1]

- **Characteristics of the study population**
  Differences in the characteristics of the patients between the two arms for comparison, as well as their treatments prior to baseline, may influence the endpoints being assessed. The FDA recommends the use of an ECA population that is comparable to the treated trial arm through the adoption of appropriate eligibility criteria. In situations where the two arms are not concurrent, efforts should be made to "*ascertain that the diagnostic criteria for the condition of interest and other relevant baseline factors, including the approaches used to ascertain data on such factors have not changed during the time of data collection.*" The recommendation is that the eligibility criteria used should be capable of facilitating the selection of similar patients in both the trial and the ECA.

- **Attributes of the treatment**
  The FDA also emphasizes the need to describe the proposed steps for handling important imbalances between the two arms on factors related to the treatment of interest as these can compromise the validity of treatment effect estimates. These may include adherence, dose, timing of initiation, duration of treatment, additional treatments, healthcare delivery, and provider or health system.

- **Index date**
  Another important determinant of comparability of the ECA is that of differences between the two arms in the determination of the index date (i.e., the start of the observation period for assessing endpoints in the ECA), which may lead to biased effect estimates because of possible "immortal time." This problem is specifically identified by the FDA as likely when the "*index date is not established appropriately across compared arms in an externally controlled trial.*"[1] There is, therefore, a need to design the ECA such as to minimize the impact of this bias, which is particularly important for endpoints that involve survival and time-to-event analysis.

- **Assessment of outcomes**
  To address the problem of bias, such as selection bias, detection bias, information bias and other confounding factors that may result from the lack of blinding in the assessment of treatment effect on certain outcomes, the FDA has recommended several processes for enhancing the comparability of data from the two arms. These include the adoption of processes that can facilitate consistency in the assessments of the endpoints, such as the involvement of independent adjudication through blind assessment of suitable endpoints and the various associated criteria involved. One of the main challenges in this respect is that of differential capture of intercurrent events, a problem that may impair the interpretability of the treatment effect on the outcome. A common example is where data from routine clinical care are not accurately captured or some important information is either missing or incomplete, such as additional treatments received by patients in the ECA.

Statistical analysis plan considerations

In an externally controlled clinical trial, the statistical analysis plan (SAP) should describe the various types of analyses of interest to the single-arm trial, namely, all the endpoints, the required sample size at a pre-specified statistical power, the overall type I error probability, and plans for controlling for the different types of bias. The SAP should also include a strategy for the following: (1) handling missing data, including sensitivity analysis where applicable, (2) addressing the problem of data misclassification of its varied forms in the ECA, and most importantly, 3) a strategy for addressing the problem of intercurrent events, including missing data as a result of such events, which may interfere with the measurement of endpoints and estimation of treatment effect.

All the assumptions associated with the proposed analytic approaches should be explicitly described in the SAP, which should also include a plan to conduct sensitivity analyses and model diagnostics to ascertain the validity of each assumption. For example, the proportional hazards assumption of the Cox regression model may not hold for some covariates. In such settings, we may need to test for the validity of the assumption to identify the time-varying covariates and conduct sensitivity analyses to adequately account for the possible impact of missing values, which may be related to the survival outcome of interest. The FDA cautions against the use of any analytical framework that requires assumptions that cannot be substantiated. The guidance document recommends that the details of the SAP be discussed with the FDA prior to the initiation of the trial. In this regard, the SAP is expected to propose the analytical steps for evaluating the actual comparability between the two study arms on important covariates.[1]

Real-world data considerations

Although, in general, data from clinical trials may offer some advantages over RWD sources for single-arm trials with an ECA, the focus of this white paper is on the use of patient-level RWD as an ECA. The critical determinants of comparability between the trial data and the ECA data include the eligibility criteria, treatment administration, patterns of care (e.g., location of treatment sites), recording of concomitant medications, and assessments of adverse events and endpoints. The most challenging externally controlled trials are those that include a historical ECA because of the different time periods between the two arms and changes in the assessment and management of the disease between the periods.

In general, the appropriateness of a historical ECA depends on the ability to control for those biases, which could limit the interpretability of the comparisons. In this regard, the impact of limitations due to period differences may be minimal, where the standard of care of the patient population has not changed noticeably over the study period. Indeed, some of these biases may be mitigated in certain situations where the disease course is predictable, and the treatment effect is dramatic.

In cases where the natural history data exist and are part of the general medical knowledge on the disease course, then a baseline control study design can be used because the pathophysiology is well understood. The FDA guidance document cites tumors as a good example of a disease that is known to have a high probability of progression over a defined period and yet does not shrink in the absence of treatment.

Other sources have suggested that, in certain circumstances, data from disease natural history study may also serve as an appropriate untreated ECA to a single-arm trial of a test drug.[6,7] In some settings, such as studies involving long-term follow-up, a more contemporaneous cohort may not offer more benefit because such could adversely affect the number of patients available for the ECA.

There are various statistical tools for further minimizing the impact of the bias associated with historical data and, if applicable, these should also be described in detail in the SAP. Regarding the suitability of ECA data, it is important to acknowledge that the availability of a dataset containing patients with the disease of interest does not guarantee the availability of sufficient information on the relevant clinical characteristics. In this regard, screening tools have been developed to help sponsors prioritize resources and explore the feasibility of using an RWD approach.[15,16]

Additional considerations for assessing comparability with real-world data

We end with the following additional considerations:

- **Time periods:** clinical care may change over time in the following aspects: (1) standard of care for the condition of interest, (2) types of treatments, (3) supportive care regimens and (4) criteria for determining disease response or progression
- **Geographic regions:** variations in standards of care and other factors (e.g., access to care) across geographic regions and healthcare systems are possible and these can result in bias as they affect health-related outcomes. A balance of patients across geographic regions and healthcare systems may help reduce the impact of the bias
- **Social determinants of health (SDOH):** variations in economic status, access to education (including quality), and others such as social support and community engagement can result in bias. A balance of patients on the SDOH factors may help reduce the impact of the bias
- **Diagnosis:** variations in the criteria used to establish a diagnosis between the two arms can also result in bias. Efforts should be made to ensure the diagnostic standards used are comparable (i.e., having been conducted and reported equally across the compared arms)
- **Prognosis:** the prognostic indicators for the patients across the two arms should be of sufficient similarity to permit an unbiased assessment of the treatment effect. However, there is an inherent assumption of sufficient knowledge of the relevant prognostic factors, which are usually based on demographic and clinical characteristics
- **Treatments:** it is useful to assess whether the ECA can be meaningfully compared to the treatment arm based on the key attributes of the treatment, such as the drug formulation, dosage, route of administration, timing, frequency, duration, and discontinuation and adherence, among others
- **Other treatment-related factors:** differences between the two arms which can also threaten an assessment of the drug-outcome association include the following: (1) previous treatments received (including lines of therapy), (2) concomitant medications and (3) predictive biomarkers (e.g., genomic testing) related to the treatment
- **Follow-up periods:** the definition of the index date should be consistent between the two arms and the duration of follow-up periods should be comparable
- **Intercurrent events:** the relevance of such events across the two arms should be assessed and should include the use of additional therapies during follow-up
- **Outcome:** the endpoints used should be reliably and consistently measured across the two arms. This can be enhanced by using the following: (1) common definitions for the endpoints, (2) suitable RWD and (3) the same criteria for the evaluation and timing of endpoint assessments across both arms
- **Missing data:** the extent of missing data, especially in the ECA, should be assessed a priori (i.e., when such data are available) to examine its potential impact

How Fortrea can support your externally controlled single-arm trial

When planning a single-arm trial, efforts should be focused on identifying and bridging any gaps in the epidemiology of the disease of interest. Our team of RWE scientists at Fortrea has prepared an internal toolkit of specific strategies to help ensure success, including a pragmatic pathway for implementing the critical "themes" that constitute the FDA's recommendations.

Designing an ECA for a single-arm trial requires identifying and addressing (1) the potential sources of bias and (2) the important intercurrent events, which may affect the interpretability of the endpoints. The RWE scientists at Fortrea have the necessary expertise in the handling of RWD. For example, in addition to our toolkit, which is presented as a checklist to inform decisions at the planning stages of a single-arm trial with an ECA, our scientists have also developed an innovative and straightforward analytical approach for handling the problem of immortal time bias, which is one of the major challenges of an ECA in such trials as highlighted in the FDA guidance document.[17]

Although the FDA has recommended that they should be consulted prior to the initiation of a single-arm trial, evidence from some of the successful applications suggests this step may not be necessary in certain settings, for example, in trials of therapies for rare diseases, especially those, that are intended for orphan drug application and are without serious safety issues based on data from the associated preclinical studies.[18] Nevertheless, Fortrea strongly recommends that both the protocol and SAP for the ECA aspect of the study be submitted to the FDA's relevant review division, prior to initiation of at least that aspect.

Our team is uniquely equipped with the necessary expertise, experience and operational capabilities to provide services in both the planning and conduct of such trials, including feasibility assessment of an ECA, recommendations for the type of RWD suitable for the ECA, support for communications with the FDA and trial diversity planning, as relevant.

Learn more about how we can work alongside your team to provide strategic advice and accelerate your product development.

Fortrea consulting services

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