Let's talk Re@l: Let's talk external controls!

A quick dive into the latest FDA guidance, SIG discussions and the industry's experience so far

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One of the most well-known uses of RWD is in forming a comparator group from outside of the trial setting to contextualize what we see in a single-arm trial setting. These externally controlled designs have been particularly helpful in evaluations of treatments for indications where RCTs have been challenging to set up from ethical or practical perspectives, yet with notable unmet medical need - such as rare diseases or severe diseases with poor outcomes. As the industry's experience with these studies has grown, the FDA has recently released draft guidance on how to leverage external controls (FDA, February 2023). This is the latest addition to their series of RWE-related guidance documents issued by the FDA as part of their program evaluating the potential use of RWD in drug approvals; and provided our RWD SIG with another opportunity for lively discussion and exchanges of ideas.

The FDA draft guidance release - an opportunity for lively discussion

The overall response to the draft has been positive and it has been warmly welcomed by the group. It is well-structured and filled with helpful nuggets to pay attention to if considering setting up such a study. The following statement from the guidance summarizes the FDA perspective quite nicely:

"although unmeasured confounding, lack of blinding, and other sources of bias cannot be eliminated in externally controlled trials, an assessment of the extent of confounding and bias, along with analytic methods to reduce the impact of such bias, are critically important in the conduct of such trials."

At its core, the evidence we derive from externally controlled trials is non-randomized. Hence, the comparability of the treatment and control groups is key – from the characteristics of the patients through to the details of the treatment received, designation of time zero* and the assessment of the outcomes.

*from when to start follow-up and assessment of the study endpoints in the external control group

What have we seen so far? Lots to learn from experience

The draft guidance builds upon the experience we have accumulated as an industry and there are now plenty of examples out there, from which we can learn. Fellow SIG member, Rima Izem, and colleagues have recently provided a comprehensive overview of FDA-approved applications that included patient-level RWD as external controls (2022). As you might expect, the experiences are mixed, with varying levels of success in terms of getting the RWE in the product label, and they illustrate that such contextualization of single-arm trials is not easy – but still possible!

A textbook example with some of the pitfalls to look out for, is that of Selinexor for the treatment of adult patients with relapsed or refractory multiple myeloma (RRMM). The new drug application for *Selinexor* (2018) included data from a multicenter, open-label, single-arm trial (STORM) and electronic health records from patients identified in the Flatiron Health Analytic Database (FHAD) – intended to serve as a control group for comparison of overall survival. The initial submission was followed up by two information requests, identifying various methodological issues with the external control group

comparison (see Table 1) and ultimately leading to these data being excluded from the approval decision-making process.

Table 1: Summary of FDA-identified limitations of RWD-based external control group included in submission package for Selinexor

Limitations identified	FDA comments on RWD part of results
Small sample size	After key inclusion/exclusion criteria were aligned, the number of eligible patients in the FHAD set reduced to 13 - likely too small to be representative and corresponding analyses underpowered to show a difference between the groups
Confounding	Imbalances between treatment groups were not adequately accounted for in the design or analysis phases, which likely resulted in confounding bias, primarily favoring survival for the STORM cohort.
Selection bias	More stringent exclusion criteria for trial patients such that these were more likely to be healthier than controls. For example, the Applicant cited real-world OS of patients with penta-exposed, triple-class refractory MM as 3.5–3.7 months; however, patients with less than 4 months life expectancy were excluded from STORM.
Immortal time bias	Time zero defined as date upon which a patient failed his or her last treatment – by design, STORM patients are required to have lived long enough to enroll in the study, i.e., immortal person-time between failure of prior therapy and randomization. No such requirement applied to the FHAD patients.
Performance/misclassification bias	Potential differential treatment misclassification as a result of the differing inclusion/exclusion criteria for the STORM and FHAD cohorts (e.g. 27/64 FHAD patients had no subsequent treatment after time zero so should have been excluded).
Missing data	Substantial missingness of key confounding factors, among others, ECOG was missing in 31% of control patients and baseline tumor stage status mostly unknown (65-78% II/Unknown).
Lack of pre-specification	Without having reviewed and consented to a protocol and SAP, FDA cannot be certain that the protocol and SAP were pre-specified and unchanged during the data selection and analyses. This uncertainty and the knowledge that subsequent unmasked analyses have been performed could lead to overly optimistic conclusions.

One success story is that of *cerliponase alfa* (Brineura, 2017) in the rare disease indication of late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), which was approved based on comparison with an external control group derived from real-world registry data. This approval entailed “many iterations of communication” between FDA and the applicant; as well as revision of the primary efficacy endpoint, which was based on the CLN2 rating scale, due to differences in how the scale was assessed for the two data sources and in the FDA’s words: “to ensure that an observed change was an actual change and not due to measurement error”. Ultimately acceptable RWE was established and is now included in the product’s label.

RWD SIG feedback on the draft guidance

Back to the guidance, the main comments from the RWD SIG are as follows:

- To expand the present scope of the guidance to include points on how external control data can supplement an RCT control arm.
- Although submission of only summary-level data is out of scope of this guidance, it would be useful to clarify that the FDA does not discourage the use of summary-level estimates in place of patient-level data, often used, and incorporated in the Bayesian borrowing framework when using historical RCT data as a comparator group.
- To clarify FDA position on the use of externally controlled designs to evaluate non-inferiority; whilst discouraged for evaluating effectiveness, external controls may be useful in assessing non-inferiority with respect to safety.
- Practical concerns about having the externally controlled study protocol finalized prior to recruiting patients into the single arm trial yet ensuring similarity between the treatment and control arms.
- Lack of clarity on level of evidence expected to justify the list of confounders or prognostic factors. How much justification is needed a-priori? And can this be expert-driven or data-driven?

For more details, the comments from EFSPI are available here, one of 180 sets of comments that have been submitted to the guidance docket. We look forward to seeing the FDA response, continuing to learn as an industry and the continuing developments on this topic.

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