Rare diseases challenge: no or insufficient patients in a control arm

Rosa Lamarca[1]

[1]Alexion Pharmaceuticals/AstraZeneca Rare Disease business unit/Quantitative Sciences

In rare diseases, single-arm, non-randomised, open-label trials are frequently conducted, mainly due to ethical reasons or the study being unfeasible as patients reject to participate. However, there are some inherent limitations in this type of designs, for example, time-to-event endpoints and patient reported outcomes are not interpretable without a control arm in the study. There are other circumstances, where a randomised control trial is doable but the number of subjects in the control arm are insufficient. The use of external data (clinical trial data or real-world data) appears as a way to overcome these limitations and improve the efficiency of clinical trials.

A critical step in bringing external data is to ensure that the external data is comparable to the study population in terms of study entry criteria, in particular to measured baseline prognostic/ confounding variables. Ideally, both external data and study population should be exchangeable with each other. There are several frequentist methodologies to adjust for differences in baseline prognostic/ confounding factors, such as, the propensity scores (Rosenbaum and Rubin, 1983) based on matching, stratification, inverse probability of treatment weights, or covariate adjustment on propensity score methods. These methods balance the prognostic factors, then the comparison of outcomes between the treatment groups yields an unbiased treatment effect estimate, as long as all the confounding variables are included in the propensity score model.

Also, Bayesian methods have been developed to borrow information from external data by creating an informative prior distribution. The prior can be derived based on different approaches such as the meta analytic predictive method.

It is important to note that the type I error may be inflated by incorporating external data as a nonrandomised comparison may introduce bias due to unmeasured confounding covariates. Therefore, simulations should be carried out to evaluate the operating characteristics when including external data.

Regulatory agencies have not ignored this situation and have taken some initiatives and released corresponding guidance with recommendations when designing externally controlled clinical trials. However, the use of external controls is not mature enough yet and interactions with regulatory agencies are advisable at the time of the study design.

Keywords: Rare disease, single-arm clinical trial, external data, propensity scores, Bayesian methods.