Oncology trial data features

Longitudinal study involving active disease treatments plus patient follow-up

Oncology trials are often characterized by longitudinal follow-up, rapid decline of available PRO data, and the need to quantify data resulting in meaningful interpretation.

Post-treatment follow-up

- Continued PRO assessment post-treatmentvä quiero información sobre la solicitud de tratamiento de fecha.

Hypothesized effect

- What is the expected change in the outcomes given the intervention?

Interpretation of effects

- For time to event data, analysis is largely dependent on a predefined model, i.e., the patient-specific PRO score at baseline.
- The interpretation of what is a meaningful effect is dependent on the context of the proposed model for endpoint analysis.

Multidimensional Outcomes

- Many PROs used in oncology trials are multidimensional in nature.
- Total scores can be a poor representation of the underlying changes in component scores.
- Interactions among various component scores may be important.

Missing data

- Missing data at subject level, questionnaire level, item level
- A critical discussion of the number, timing, pattern, reason for and possible implications of missing values [by time trend analysis] should be included in the discussion of results.
- Sensitivity analyses should be performed for main PRO analyses.

Subgroups

- The effects of the studied treatment on subpopulations of interest
- The analysis should be conducted post-hoc.

Methods for analyzing patient-reported outcomes in oncology trials

Analyses fall into two main branches of statistical analysis: methods of mean and mixed-type models. Analysis of group means, either at selected time points or longitudinally using repeated measures models or mixed-effects models are used to provide means between treatment groups in PRO endpoints. Survival-based analyses are used to show time to a specific within-patient event, for example and as mentioned in both US and European guidelines, the time to progression or death.

Subgroup analysis

- Mean score or change at selected time points

Oncology trials have been traditionally analyzed by selecting time points of interest and comparing mean scores or mean change scores between treatment arms by ANOVA/CANOVA type methods. Such analyses are limited to available data at the considered time point and unbiased inferences are made under the assumption that missing data are missing at random (MAR). However, this is a restrictive assumption in oncology trials due to the high number of missing data, particularly if these are stratified across groups.

Single value imputation methods

Simple imputation techniques such as last observation carried forward (LOCF), linear extrapolation, and imputed worst score replacement are often performed in order to explore the estimated treatment effect under simple missing data mechanisms. However, these forms of single value imputation may not realistically simulate real life missing data. Moreover, the assumption of treatment effects (imputed values can be overly optimistic), and others, underestimate standard errors and confidence interval widths.

Longitudinal approach of outcomes

The requirement for complete data can be relaxed by using repeated measures or mixed-effects models, allowing for all available data to be used and therefore reducing or eliminating the need to perform additional imputations or sensitivity analyses. Properly developed patient-reported outcomes (PRO) play a valuable role in capturing what is important to patients, allowing for better communication of treatment value to patients and caregivers, patients, and healthcare providers.

Pattern-mixture models

The general concept of the pattern-mixture model is to estimate the effects of the pattern of missing data. Results can then be combined as a function of weighted average of parameter estimates over the different patterns. Pattern-mixture models may be appropriate when data are available only for a subset of the population with analyzable data. If the novel treatment can be assumed to increase progression-free survival (PFS) and overall survival (OS) and incur higher treatment-related costs, then under the assumption of missing not at random (MNAR) the results can be used to explore the impact of the pattern of missing data. As with traditional oncology trial endpoints OS and PFS, the specification of censoring and events allows PRO data to be imputed under the assumption that patients are censored at a defined time point. They rely on careful selection of the event definition (death, group event or censoring) for the analysis.

Conclusion

PROs can be successfully implemented into drug development trials and can serve to inform regulatory approval, product labeling and healthcare decision makers.

It is recommended that sponsors carefully consider the characteristics of the data they are collecting and plan their analyses early in order to accommodate the potential limitations of PRO data. A common mistake is to characterize a number of features, mainly longitudinal analysis in the presence of missing informative data, and options are available to generate meaningful PRO evidence.

Summary points

PRO data can add valuable information in the assessment of the overall benefits and toxicity of oncology products assessed in the condition that their analysis is conducted rigorously.

PRO strategy should be carefully considered early with the endpoint in mind. Analyses should aim to quantify data resulting in meaningful interpretation.

Oncology trials are characterized by a substantial follow up, rapid decline of available PRO data, post-treatment follow-up data, cross-over, open labels/stratified survival.

Traditional analyses are often inappropriate or limited due to characteristics of oncology trial data. Sensitivity analyses should be performed testing the robustness of the treatment effect under different model assumptions in order to aid interpretation.

References