

Approaches to Integrated Safety Analyses

Rosenkranz, G

Biostatistics and Statistical Reporting, Novartis Pharma AG, CH-4002 Basel

The routine analysis of adverse events from clinical studies is done on a study by study and an event by event basis: for each event classified according to a list of so-called preferred terms, the difference of the proportion of subjects experiencing the event is presented, sometimes with a confidence interval or a p-value or both. This presentation ignores the structure behind adverse event data, namely any grouping according to system organ classes, it does not account for any correlations between those data nor for multiplicity issues.

Attempts to group adverse event data according to physiological criteria have been made in the past, however, to our knowledge, none of these attempts are widely used. Only during the last years have methods been developed that impose some structure on adverse events data. Interestingly enough, this was first done for spontaneously reported events that happen after the approval of a new drug, and only later for adverse events occurring in clinical studies. This talk will briefly review these methods, but focus on the analysis of data from clinical studies.

The talk will mainly investigate the applicability of mixed effects models to the integrated analysis of adverse events. By integrated we mean that data stem from different studies (from different phases or in different indications) comparing different regimen of the drug under development with placebo or active comparators. The main reason for integrated analyses is to borrow strength across different types of events and regimen. By doing so, point estimates based on a very small number of events will usually shrink compared to a naïve approach. Currently we consider aggregated data on the system organ class level to reduce computational burden. The approach can be generalized to include further covariates like dose, demographics, indication etc. The methodology will be illustrated with an example.