Missing values in clinical trials: Regulatory requirements and two examples

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Missing values are a common problem in clinical trials, in particular with out-patients. The relevant guidelines (ICH-E9, CPMP-PtC) prescribe that the problem has to be addressed in submissions of data for registration. However, they do not intend to give any guidance regarding which methods should be used or are preferred, except for obvious cases.

Current practice includes only elementary methods such as Last-observation-carried-forward and is often based on incomplete datasets, e.g. randomised patients with no on-treatment data or no baseline data are excluded. The problem with these simple approaches is to show that the non-availability of data does not carry any information, and that carrying forward data or exclusion of patients does not introduce bias into the estimator of the treatment effect. We bring 2 examples where an analysis according to current practice obviously is not sufficient. In the one of the examples, several options, including model-based multiple imputation, are followed up and recommendations are given.

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