Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials

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There has been much debate in the pharmaceutical industry over the last few years about the handling of missing values in longitudinal trials. On the one hand, the regulatory agencies are increasingly critical of poor design and analysis that do not assess the potential impact of patients dropping out of trials; and on the other hand, many industry and academic statisticians are increasingly strident about some of the long-used methods that the regulators prefer and have mostly insisted on. The pharmaceutical trade association in the USA, PhRMA, included this area in a recent initiative to improve efficiency of late-stage clinical research, and set up a cross-industry team to make recommendations. Groups in several companies have also been pushing for change, and investigating improved strategies for dealing more adequately with the issues that arise from missing data in regulated trials. I shall summarize the recommendations of the PhRMA team, and discuss in particular the use of mixed models for repeated measures and of the method of last-observation-carried forward, with examples from trials in the neuroscience therapeutic area. I will also outline how a primary analysis should be bolstered, when there is substantial drop-out, by sensitivity analysis to demonstrate the potential effect of non-ignorable missingness.

Main references

1. Mallinckrodt CH, Lane PW, Schnell D, Peng Y, Mancuso JP. Recommendations for the primary analysis of continuous endpoints in longitudinal clinical trials. *Drug Information Journal* (accepted).
2. Lane PW. Handling drop-out in longitudinal clinical trials: a comparison of the LOCF and MMRM approaches. *Pharmaceutical Statistics* (early view).