HANDLING DROP-OUT IN LONGITUDINAL CLINICAL TRIALS: A COMPARISON OF THE LOCF AND MMRM APPROACHES

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The paper chosen for presentation in this session reported a study comparing two methods for handling missing data in longitudinal trials. I will first describe how this issue is currently handled and perceived in a pharmaceutical company subject to regulatory scrutiny, and thus explain the motivation of the study. It compared the last-observation-carried-forward (LOCF) method with one based on a multivariate or mixed model for repeated measurements (MMRM), using data sets simulated to match six actual trials. This involved imposing several drop-out mechanisms, and compared the methods in terms of bias in the treatment difference and power of the treatment comparison. I will outline the simulation process, and concentrate on the conclusions: that the bias of LOCF could be in either direction, was generally much larger than that of MMRM and caused a greater loss of power. Use of the LOCF method is therefore likely to misrepresent the results of a trial seriously, and so is not a good choice for primary analysis. In contrast, the MMRM method is unlikely to result in serious misinterpretation, unless the drop-out mechanism is missing not at random (MNAR) and there is substantially unequal drop-out. Moreover, MMRM is clearly more reliable and better grounded statistically. Neither method is capable of dealing on its own with trials involving MNAR drop-out mechanisms, for which sensitivity analysis is needed using more complex methods.

I will put the results of the study into context by summarizing the recent report of a team, of which I am a member, set up by PhRMA (Pharmaceutical Research and Manufacturers of America) to make recommendations on this issue. This drew on many research publications, and on the experience of many companies, coming to broadly the same conclusion about the need to move on from the traditional and simplistic technique of LOCF, and laying out a rational strategy for investigating the effect of missing data in regulated trials.