INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

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Comments regarding CPMP/EWP/1776/99 draft: "Points to consider on missing data", London, 25 January 2001.

General

This is a reasonable document bearing in mind that the concept of missing data is still a developing field in which there is so far no general consensus. However, the result is inevitably a guideline without much guidance.

The 'Introduction' describes different degrees of data incompleteness from the case of measurements only being available at baseline (patient dropped out after initial assessment) to the situation of say a single missing value (patient not a drop-out). However, the guideline in general seems to address mostly the more serious case of a 'whole' patient dropping out. ***It may be useful if more distinction was made between these situations within the guideline and guidance given accordingly***. There is of course a theoretical framework classifying drop-outs as either 'completely at random', 'at random' or 'informative'. It might be useful to acknowledge this in the guidance by specifically referring to it in 4.4 (Sensitivity analysis).

It is stated twice (3rd paragraph in the 'Introduction' and the opening sentence in Section 3.2.2) that a "full set analysis requires the imputation of values for the unrecorded data / to those data that have not been recorded" (respectively). It is suggested that this is too strong and that inserting the word 'generally' in front of "requires" would be appropriate as for example, an 'end-point' analysis (a valid full set analysis) does not rely on imputation even though it is synonymous with a last observation carried forward analysis.

Specifics

2.1 Power and Variability

The real problem with changes in variability due to missing data is not just that it "could lead to an underestimate in variability" but that in fact as a consequence the confidence interval will be biased.

We therefore suggest adding to the last sentence in 3rd paragraph: ***"and hence bias the confidence interval for the treatment effect"***

3.1 Complete case analysis

Last sentence states that complete case analysis "cannot be recommended as the primary analysis in a confirmatory trial". In view of the statement in ICH E9 (5.2.3 Roles of the Different Analysis Sets) that "in an equivalence or non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully" by implication the above sentence should be toned down a little to, for example; ***"cannot generally be recommended as the primary analysis in a superiority confirmatory trial"***.

3.2.1 Scope of imputation

The section opens: "As missing values may affect different types of variables...".
It is the reason for 'missingness' that affects different types of variables not the missing values themselves.

3.2.2 Methods for imputation of missing data

LOCF is 'translated into "last value analysis, last value carried forward". Alternatively "last value analysis" may be termed '***endpoint analysis***' whilst "last value carried forward" perhaps should be termed '***last observation carried forward***' (which is the direct abbreviation).

LOCF is said to be "less acceptable" in situations where measurements are not expected to be constant over time. In the example given, Alzheimer's disease, where the patients' condition is expected to deteriorate over time, LOCF is still conservative if the missing values are only in the control group.

It might be appropriate for the guideline to include a statement to the effect that single imputation methods run the risk of biasing the estimate of the standard error downwards because in the second stage of analysis no distinction is made between real and imputed data. In this, they differ from the EM algorithm and multiple imputation approaches.

4.1 Avoidance of missing data

To the list of factors regarding the maximum number of missing values that could be acceptable could perhaps be added ***(d) the treatment modalities***.

4.2 Design of the study. Relevance of predefinition

The term "the study hypothesis" in the 2nd paragraph should be changed ***to 'study working hypothesis'*** to avoid confusion.

4.3 Analysis of missing data

The advice given in this section is of debatable relevance. If a covariate is prognostic of outcome, it

should be in the model anyway. If it is also prognostic of drop-out this will help to satisfy the missing at random assumption but strictly speaking it is its prognostic relevance that is important. If the covariate is not prognostic of outcome, there will be little point in fitting it anyway. The only case not covered by this approach is where a covariate by treatment interaction is predictive of drop-out: for example if elderly patients in the placebo group tend to drop out of the trial. However, the section as currently worded does not make this clear.

4.4 Sensitivity analysis

It is stated that "Sensitivity analysis ... will help to justify the choice of the particular method applied". ***We suggest to insert the words 'a priori' in front of "choice"***.