



INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

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Comments regarding CPMP/EWP/2863/99 draft: “Points to consider on adjustment for baseline covariates”, London, 14 December 2001.

General

This document in contrast to previous PtCs seems rather prescriptive. While some professionals may see this as beneficial we believe that the real ‘strength’ of these documents lie in their discussion of the issues, and as many points are and may continue to be controversial, we would prefer a less authoritative document. In particular, the message that there can be no stratification without including stratification factors in a (primary) model seems unnecessarily strong. A pragmatic view would be to stratify for factors not necessarily known to be prognostic but maybe suspected to be so in which case it might improve the ‘comfort feeling’ of having balanced groups. The advantage of reporting on a simple model should never be underestimated.

The document suffers from a degree of redundancy generated by the format being divided into two main sections, planning and report. An improved structure might result if this division was abandoned and replaced by a format which focused on the ‘issues’ within which reference could then be made to the importance vis-a-vis planning and/or reporting.

The term sensitivity analysis is generally broader than as used in this document. It should be made clear that using the term in this PtC is not intended to refer to its broader meaning.

Some discussion of the case of missing values of baseline covariates would be desirable.

The language needs to be improved and the document carefully proof-read to avoid some of the irritations of the current version. Words like “proper” continuous baseline or “strong” prognostic variable should be avoided – a baseline is either continuous or not; a prognostic variable is either important/relevant or not.

Specific Points

1. Section II.1.1

Last sentence of the last (3rd) paragraph might sit better at the end of the first paragraph.

2. Section II.1.5

If ‘% change from baseline’ is used (not uncommon) in stead of ‘actual change from baseline’ the relationships discussed are less straightforward. Some discussion of this situation may be helpful. It is recognised however, that if ‘% change from baseline’ is in stead considered as a ratio and log-transformed (which implies using log-baseline as covariate) it accords with the guideline (not withstanding any discussion of the transformation issue).

3. Section II.2

If the structure of the document remains (see our general comments above) the last (4th) paragraph of this section might be more appropriate under ‘reporting’.

4. Section II.3

It is suggested to amend the last sentence 2nd paragraph to: “Clinical considerations, such as the clinical relevance of a given covariate, and statistical aspects, such as the use of partial correlations *determined from previous trials* rather than pairwise correlations, could be taken into account to achieve this” (words in *italics* are additional to the present version of the document).

It is suggested to amend the last sentence 3rd paragraph to; “However there may be occasions, such as when the interval between baseline measures is substantial compared to the interval from baseline to outcome *or such as when a prior treatment is being 'washed-out' during the baseline period*, where it may be appropriate to use the last baseline measure only” (words in *italics* are additional to the present version of the document). Alternatively, leave the sentence out all together as the guideline is in danger of becoming too detailed.

5. Section II.4

The last paragraph (5th) last sentence suggests an action when outlying variables may be expected. Action when outlying variables are not expected but found could also be discussed.

6. Section II.5

The recommendation in the last sentence of the last (3rd) paragraph: “... it should be sized so that adequate power is achieved in each subgroup of clinical interest” is not included in the ‘Conclusions’ (section IV). Some discussion of why this is not a good strategy could be added here.

7. Section II.6

The sentence “... an analysis unadjusted for covariates should be proposed systematically ...” seems unnecessarily strong; change it to: “...an analysis unadjusted for covariates could be proposed ...”.

It is suggested to amend the last sentence to: “Similarly, if a categorical covariate has been used in the primary analysis, the prespecification of an alternative categorisation for use in a sensitivity analysis would add credibility to the conclusions *in situations where multiple possible categorisations are apparent*” (words in *italics* are added).

8. Section II.7

If the 1st sentence in the last (2nd) paragraph is changed to: “It should be emphasized that even when stratification is carried out to balance the treatment groups with respect to a given covariate, adjusting for that covariate in the analysis might still lead to *a reduction in the variance of the estimate of the treatment effect and further reduce or eliminate potential bias in the estimate of treatment effect due to any imbalance of the covariate at baseline*”, it renders the rest of the paragraph redundant.

9. Section III.1

How can a statistical test be descriptive? Well, only in the sense that it is not a test of a meaningful hypothesis. Should we not therefore abandon it all together?

10. Section III.2

It is suggested to amend the 1st sentence in the 1st paragraph to: “If the key covariates are expected to be strongly correlated with the primary outcome and the functional form of the primary model were specified clearly in the protocol *or formal analysis plan*, together” (words in *italics* are added).

It is suggested to amend the 1st sentence of the 2nd paragraph to; “Conversely, if the analysis model and the method of adjustment for covariates were not specified unambiguously in the protocol *or formal analysis plan*, then many competitive ...” (words in *italics* are added).

Last (4th) paragraph; strong evidence of a treatment by covariate interaction should not automatically invalidate a primary analysis (without the interaction term in the model) as one would expect the treatment effect to be convincing in one or more subgroups (see also recommendation in II.5).

11. Section IV

Second paragraph; the following part of the 1st sentence of the 2nd paragraph seems superfluous and may not generally be correct: “... and consequently in an increase in expense and time for drug development ...”.

4th recommendation: Change “... must be ...” to “may be”.

8th recommendation: Add “or formal analysis plan” after “... protocol”