European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

RECOMMENDATION FOR THE REVISION OF THE POINTS TO CONSIDER ON MISSING DATA (CPMP/EWP/1776/99)

AGREED BY THE EFFICACY WORKING PARTY	September 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	13 December 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2007

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KEYWORDS	*Missing data*

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1. INTRODUCTION

Missing data are a potential source of bias when analysing clinical trials. The Points to Consider on Missing Data was adopted by CPMP in November 2001. It is considered timely to review the issues covered in the document and it is likewise considered necessary to revise certain aspects of the document as discussed below.

2. PROBLEM STATEMENT

Handling missing data remains a problem for the majority of clinical trials. In many marketing authorisation applications the handling of missing data is poor. There is often little or no critical discussion of the pattern of missing data or patient withdrawals in either the protocol or the study report and frequently only one sensitivity analysis addressing the implications of the missing data and the chosen imputation strategy on the trial results is provided. On many occasions no sensitivity analyses are conducted and no justification provided for their absence. When sensitivity analyses are provided they are not necessarily tailored to the missing data pattern observed. It seems necessary therefore to emphasise the importance of summarising and critically appraising the pattern of dropouts (including timing of withdrawals as well as reasons for withdrawal) when results of a study are presented in a regulatory submission. This is an area where regulatory submissions could clearly be improved, facilitating assessment and leading to better regulatory decision making. Embellishing the current guidance should help to raise the standard of submissions.

At present there exists a misconception of the regulatory view of the use of Last Observation Carried Forward (LOCF) as a method for handling missing data and the situations when an analysis using this method provides a useful summary of the data. It is proposed to add a paragraph to better explain the role and the limitations of LOCF and other similar approaches, explaining that such methods can be useful in many situations, but that an LOCF analysis is not a regulatory necessity and, indeed, is inappropriate in some trials. Whilst some sponsors are aware of the limitations of LOCF, numerous sponsors employ the method without any regard to its suitability. The misconception that LOCF represents a necessary and sufficient approach to missing data should be dispelled.

Finally, the existing guideline mentions the use of ‘mixed models’ as a potential method for handling missing data. In 2001 the use of multiple imputation methods and mixed models was uncommon in regulatory submissions but mixed models in particular now appear with increasing frequency in submissions and in proposals to the Scientific Advice Working Party. It is proposed that a cautionary position is maintained toward these methods at the present time as their use is still controversial. However, the reasons for this cautionary stance needs to be more clearly explained and the section would be usefully amended to reflect the growing literature and regulatory experience with these methods since 2001.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

No major changes to the current guidance are foreseen, but it is considered meaningful to undertake a revision in order to re-focus attention on the missing data problem and to address the potential problems associated with the increasing use of mixed models, reflecting up-to-date statistical literature and regulatory experience.

4. RECOMMENDATION

The Working Party recommends a revision of the Points to Consider on Missing Data. The scope of the revision is detailed above.

5. PROPOSED TIMETABLE

It is anticipated that a draft revised CHMP guideline will be available 6 months after adoption of this document for 3 month release for external consultation, before finalisation in 3 months and adoption by CHMP in 2008.

6. RESOURCE REQUIREMENTS FOR PREPARATION

It is proposed that Spain act as rapporteur, with assistance as required from UK. A preliminary discussion between these parties should precede a first draft being presented at the Efficacy Working Party. One further presentation to the Efficacy Working Party is envisaged to discuss a revised version. No need for a formal drafting group is envisaged.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is anticipated that the revision will lead to an improved standard of regulatory submissions and hence of regulatory decision-making with consequent beneficial impact for both public health and for industry.

Other than familiarisation with the revised document, there are only minimal resource implications for application by regulatory authorities and industry, though it is hoped that through better understanding of requirements, and agreement of standards, fewer requests for scientific advice on this topic might be required and fewer objections will be raised in assessment of applications.

8. INTERESTED PARTIES

- the pharmaceutical industry (incorporating Contract Research Organisations)
- the 'statistical' community in academia
- other regulatory agencies (e.g. FDA)

The revisions might also be considered by Scientific Advice Working Party.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

There are hundreds of publications relevant to handling missing data in clinical trials. Given that this is a proposed revision, rather than an inception of guidance, they are not listed here.

Related guidelines:

- ICH E9 Statistical Principles for Clinical Trials (CPMP/EWP/363/96)