SUBMISSION OF COMMENTS ON "GUIDELINE ON THE USE OF STATISTICAL SIGNAL DETECTION METHODS IN THE EUDRAVIGILANCE DATA ANALYSIS SYSTEM"

COMMENTS FROM German Region of the International Biometric Society

GENERAL COMMENTS

- It is not clear to whom this guidance document is directed. In the Executive Summary the "stakeholders" are mentioned as the analyzers of adverse event data but it is not clear who they are. Footnote 1 on page 3/21 does not give any further indication. To the best of our knowledge there is no access to the data contained in the EudraVigilance Data Analysis System by external parties (like MAH's or academic organizations).

  In general, the draft guideline rather looks like an internal guidance for EMEA co-workers on how to use the EudraVigilance Data Analysis System properly. This notion seems to be supported by the fact that more or less the complete chapter 5 of the draft guideline reads like an extended user manual to this EudraVigilance Data Analysis System. Moreover, the EudraVigilance Data Analysis System seems to be already operational (see last sentence first para in Executive Summary, page 1 and e.g. large parts of chapter 5). If the draft guideline is thought for internal use, we wonder why it is disseminated as an EMEA guidance document to the public.

  So according to the real addressee of this document, either chapter 5 may be dropped – or chapter 5 remains and the whole document may be turned into an internal (EMEA) user manual of the EudraVigilance Data Analysis System.

- As long as the proportional reporting ratio (PRR) has been already implemented in the EudraVigilance Data Analysis System as the only measure of disproportionality (as mentioned in last sentence of the first para in the Executive Summary) there seems to be no need for a guideline on the "use of statistical methods" in the EudraVigilance Data Analysis System. If there is a software tool that only allows one specific statistic to be calculated, guidance may be required only on i) how to use the software at all ("user manual") and ii) the interpretation of results.

  For a guideline under discussion it seems to be even more worthwhile to discuss the options of statistical methods to be used for signal detection and if possible provide guidance on which one to prefer in which situation based on the detailed content of database used (if there are differences in this regard between the different statistical methods available).

As it is by far not obvious which method is preferable or even "optimal" in general for the detection of disproportionalities in the (routine) reporting of adverse events, we would suggest to provide indeed guidance on the options available and which method(s) will be preferred. In addition, there is already increasing evidence from published reports available, indicating that the PRR has considerable drawbacks as directly compared to the empirical Bayes multi-item gamma Poisson shrinker (MGPS) [c.f. 1]. In addition, there might be other measures with better statistical and decision theoretic characteristics as the PRR, although there exist not in every case published direct comparisons to the PRR yet [2, 3, 4, 5, 6]. However, the other options beside the PRR shall be critically reviewed and discussed in a document of the scope as currently expected given the title of the guideline.

- We would recommend to include a statistician in the review of the document as there are numerous inconsistencies and methodological shortcomings in the document, e.g.
    - chisquare statistic is not a measure of association
    - the threshold introduced in section 4.6 used for the chisquare statistic are not based on scientific rationales
    - the use of confidence intervals rather than test statistics should be pointed out and implemented in the tool. The consistency between test statistics and confidence intervals should be discussed.
    - the χ^2 -formula in section 5.2.2 is not correct

  Furthermore, the guideline should clearly state that beyond the request of a medical assessment, a statistical assessment is required as well.

References:

[1] Almenoff J et al. Comparative performance of two quantitative safety signalling methods. Drug Safety 2006; 29(10):875-887

[2] Puijenbroek E et al. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems of adverse drug reactions. PE&DS 2002; 11:3-10

[3] Almenoff J et al. Perspectives on the use of data mining in pharmacovigilance. Drug Safety 2005; 28(11):981-1007 – Ref. [5] in the Guideline document

[4] Rothman KJ, Lanes S, Sacks T. The reporting odds ratio and its advantages over the proportional reporting ratio. PE&DS 2004; 13:519-523

[5] Rolka H et al. Using simulation to assess the sensitivity and specificity of a signal detection tool for multidimensional public health surveillance data. Stat Med 2005; 24:551-562

[6] Moore N et al. Biases affecting the proportional reporting ratio (PRR) in spontaneous reports pharmacovigilance databases: the example of sertindole. PE&DS 2003; 12:271-281