INTERNATIONAL SOCIETY FOR CLINICAL BIOSTATISTICS

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Comments regarding CPMP/EWP/2330/99: "Points to consider on validity and interpretation of meta-analyses, and one pivotal study", London, 19 October 2000.

General

This is a sensible document which makes many reasonable points from the list of reasons for performing a meta-analysis to the idea that a meta-analysis protocol should be specified in advance of the knowledge of the individual study results, and at the same time recognising that this is not always realistic.

However, we find the title somewhat confusing. From it, one may get the impression that the document addresses meta-analysis *versus* one (pivotal) study (in a submission). However, this does not seem to be the case. The fact that 'meta-analysis' and 'one pivotal study' are addressed as separate topics should be borne out more clearly in the title. ***We suggest: "Points to consider on validity and interpretation of a meta-analysis and of a single pivotal study, respectively".***

An index, even though the document is relatively short, may nevertheless help to emphasise the separate points being made.

The specific comments below concern, in the main, matters of emphasis, but assumes that the document is meant to address two separate topics, meta-analysis and one pivotal study.

Specifics

I INTRODUCTION

The statement "the use of a meta-analysis to provide the pivotal evidence in an application will always be problematic" (start of 2nd paragraph, page 1) is too strong. The alternative to a meta-analysis in the sense of summarising data is an informal analysis. This could well be considered more problematic than a meta-analysis. We acknowledge as pointed out in the guideline that stronger evidence is sought from a meta-analysis (something appreciably lower than 5%, if significance has been assessed at 5% for the individual studies). However, this does not mean, that meta-analyses are inherently problematic. We consider that it is essential that two issues are clearly distinguished: the standard of proof and the means for assessing whether that standard has been reached.

II.1.2 TIMING OF PRE-SPECIFICATION

As mentioned earlier we support the contention that a meta-analysis should be pre-specified. Nevertheless, the main issue is that of fair summary and presentation of the results. Has the sponsor performed the meta-analysis using "utmost good faith"? Such "utmost good faith" is clearly easier to believe in, when the analysis protocol is specified in advance. Notwithstanding this, the guideline does recognise that there may be situations where a meta-analysis may be driven by the individual study results. ***We are somewhat puzzled however, to read that this is the case when seemingly conflicting results need to be put into perspective***.

II.1.3 REGULATORY PREREQUISITES OF RETROSPECTIVE META-ANALYSES

"Prerequisites for a potentially acceptable retrospective meta-analysis include" may be too strong when after listing six prerequisites it is stated that "for meta-analyses where these requirements are not fulfilled it will prove difficult to get a regulatory acceptance". For example, if (a) "some studies were clearly positive", (b) "inconclusive studies showed positive trends" and (c) "the pooled confidence interval was well away from zero", it would be strange to insist that there should be (d) "no statistical or major numerical heterogeneity". Such heterogeneity is most likely precisely where a treatment is effective. Thus, given the circumstances (a) – (c), it is almost certain that a suitable transformation of scale would succeed in removing the heterogeneity. ***We wonder if in fact it is the intention that <u>all</u> the mentioned situations must exist. If that is not the case, a reformulation is necessary.***

II.2 SELECTION OF STUDIES

The sub-headings of II.2.1 and II.2.2 could well be improved upon to better reflecting the type of study selection relevant to various types of submission. After all, an application for a New Chemical Entity takes quite a different course from that of an application aimed at providing key evidence for registering a generic, or providing further evidence for re-positioning of an existing drug. The point is that the appropriateness of a prospective or a retrospective meta-analysis could well be thought of as depending largely on the status (new/generic/registered) of chemical entity.

A point in favour of a meta-analysis of a new chemical entity is that it will usually be possible to identify all studies without elaborate literature searches. However, since a meta-analysis is a formal summary of the evidence in a submission, there is a case for the sponsor presenting a summary of exactly those trials for which he is responsible *whether or not* other trials exist and *whether or not* the regulator may in addition wish to see such trials included in a further analysis.

III.3.1 CLINICAL RELEVANCE

It is suggested that this section recognises that the same issues exist for superiority as well as for non-inferiority studies. Although 'superiority' is not mentioned per se the tenant of the paragraph is 'difference'.

III.3.2 HETEROGENEITY AND EXTERNAL VALIDITY

This section is rather obscure. There is a conflict between claiming on the one hand that studies that are too different should not be pooled and on the other hand seeking independent replication. A decision *not* to pool studies because the results are different and the protocols may differ, is only logical if two assumptions are made. First, that the difference in results is a consequence of the presumed difference in study. Second, that the potential bias-variance trade-off indicates the desirability of eliminating bias at the expense of increased variance. The difference between the results of the studies might be due to a factor other than that supposed. For example, one study may be in high-risk patients and the other in low-risk patients, but these are not factors that are allocated at random. Hence, it may be that the studies differ in some other quite fortuitous way, for example monitoring standards. That being so, unless it can be established that one study is inherently more reliable than another, it might still be a safer strategy to pool the studies, even for the purpose of making predictions for high risk and for low risk patients.

III ONE PIVOTAL STUDY

This section states that replication is the norm, but that one pivotal study will be acceptable if the evidence is exceptionally compelling. Hence it ought to be perfectly reasonable for regulators to welcome meta-analysis whilst stressing the necessity for convincing evidence.

However, from the list of reasons why two studies are better than one it rather looks as if a more general use of the compound in different settings is advised. Can we still speak about replication in this case? Even in this framework, "An indication for which no effective treatment exists" does not seem a reasonable argument for requiring more than one study.