Concept paper on the need for a Guideline on the use of Subgroup Analyses in Randomised Controlled Trials

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1. Introduction

Analysis of subgroups is important in every confirmatory trial. Subgroup analyses are used for assessment of internal consistency, to try to rescue trials that 'fail' based on the full analysis set or to try to identify patient groups with the most favourable benefit-risk profile. Subgroups may be pre-specified in the trial protocol, based on demographic, genomic or disease characteristics (e.g. sub-entities of a disease that are widely recognised within the medical community) or may materialise based on a need or desire to further explore study results. Formal statistical methods for investigating the homogeneity of the treatment effect across subgroups do exist and these are sometimes used by companies or regulatory bodies to provide re-assurance or to challenge the applicability of overall findings to subgroups. In addition, simpler (often visual) methods can be helpful in elucidating and displaying results from subgroups. In some dossiers, the investigation of results in subgroups is minimal, perhaps in fear of (possibly false) negative findings that may complicate assessment.

There is no specific CHMP guidance document on assessment of subgroup analyses. It is proposed that some important methodological considerations and assessment strategies are set out in a guidance document and some example datasets discussed.

2. Problem statement

The document will include a general discussion on the importance of subgroup analyses in randomized clinical trials. It will describe why estimated treatment effects in subgroups can be unreliable and will summarise methods available, and their limitations, for the investigation and presentation of homogeneity of estimated treatment effects. A number of specific scenarios will be described:

i) Assessment of 'internal consistency': the uniformity or otherwise of treatment effects across a range of patients recruited into clinical trials and hence the applicability of the overall finding to subgroups. Whilst many important subgroups will be therapeutic indication specific, groups that should routinely be inspected will be identified. The role of pre-specification, replication of evidence and 'biological plausibility' in the assessment of internal consistency will be discussed. Some example 'Forest' plots and strategies for assessment will be presented and the difference between qualitative and quantitative interactions explained. The paper will discuss situations where sample size considerations for clinical trial planning should consider not only the full analysis set, but also the number of patients recruited to and the duration of follow-up for subgroups that are a priori known to be of relevance and, consequently, where assessment of internal consistency will be critical to the regulatory decision.

ii) Negative conclusions from subgroups: In trials from which a positive conclusion can be drawn based on the pre-specified analyses, concern may still arise from the assessment of internal consistency over results in one or more specific subgroups and in certain instances a restriction to the indicated patient population may be discussed.

iii) Positive conclusions from subgroup analyses: A common mis-use of subgroup analysis is to rescue a trial which, formally fails based on the pre-specified primary analysis in the full analysis set. Concerns with this strategy and factors which determine the limited scenarios where exceptions might be made will be explained. Subgroup analyses are also used in positive trials to identify groups where benefit-risk is improved compared to the full analysis set, in particular where benefit is estimated to be higher, or to make additional label claims in addition to those made on the full analysis set.

For these latter two scenarios, issues relating to multiplicity adjustment for identifying subgroups, stratification, pre-specification, replication of evidence, 'biological plausibility' and reliability of estimated treatment effects will be discussed.

iv) Some trials will be initiated with the option of basing conclusions on either the full analysis set or on a pre-defined subgroup. Specific issues with this strategy will be considered in the framework of adaptive designs for e.g. pharmacogenomic biomarkers.

3. Discussion (on the problem statement)

The topics described above are important in the assessment of any randomised controlled trial and there is no specific regulatory guidance on the topic. Investigation of subgroups can be important for the assessment of both efficacy and safety.

Guidance needs to be given on situations in which industry/applicants should present results from subgroups, how such comparisons should be made (using formal statistical methods or otherwise) and in what situations regulatory authorities should require to see subgroup analyses that companies have not otherwise submitted. Regulatory authorities need to be wary about the over interpretation of subgroups yet at the same time be confident that the breadth of the indication licensed from any particular set of trial data is based on sound data and inference.

4. Recommendation

The Biostatistics Drafting Group of EWP recommends drafting a guidance document on methodological issues relating to subgroup analyses. The scope of the revision is detailed above.

5. Proposed timetable

It is anticipated that a draft guideline will be available 6 months after adoption of this document for 6 month release for external consultation, before finalisation and adoption by CHMP in 2011/2012.

6. Resource requirements for preparation

The preparation of this guideline will involve the EWP and the Biostatistics Drafting Group of EWP. It is anticipated that at least one plenary session discussions at the EWP will be needed.

7. Impact assessment (anticipated)

Analyses of subgroups are important in every marketing authorisation application. It is anticipated that this document will lead to an improved standard of regulatory assessment of confirmatory trials and improved planning of confirmatory trials by sponsors.

8. References to literature, guidelines, etc.

1. CPMP/ICH/363/96: "ICH E9 Statistical Principles for Clinical Trials".
2. CPMP/EWP/908/99: "Points to Consider on Multiplicity Issues in Clinical TrialsPtC for baseline adjustment".
3. CHMP/EWP/2459/02: "Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design".
4. CHMP/EWP/498145/06 "Reflection Paper on Gender Differences in Cardiovascular Diseases".
5. CPMP/EWP/2330/99 "Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study".
6. CPMP/EWP/2863/99: "Points to Consider on Adjustment for Baseline Covariates".