Subgroup analyses in confirmatory trials – EFPIA perspectives

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Disclaimer (Chrissie Fletcher)

* The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of Amgen.

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Overview

- Introduction
- Key clinical considerations in subgroup analyses
- ‘Top 4’ priority areas of comments
- Other important aspects raised in comments
- Conclusions

Introduction

- 14 companies provided comments
  - 77 pages → 42 pages (consolidated)
  - 10 pages of general comments
  - 32 pages of specific comments on text
- Represents a consensus view agreed by EFPIA (Clinical Development Committee)
- EFPIA are pleased to participate in the workshop and share the Industry comments
- Value of guideline
  - An important and complex topic
  - Informative **for Industry** and Assessors

Key clinical considerations

- Subgroup analyses are an integral part of clinical development
  - Identification of relevant subgroups in planning of confirmatory trials based on biological plausibility
  - Standard exploratory subgroups (e.g. demographics, renal function)
  - Key subgroups usually discussed with Regulators (e.g. scientific advice)

- Focus of guidance appears to be on applications with a single confirmatory trial
  - Limitations of subgroup analyses should be addressed when there is only one confirmatory trial
  - Value of pooled analyses for applications with multiple confirmatory trials should be addressed more specifically

Key clinical considerations - what is the overall goal for subgroup analyses?

- Is it to demonstrate consistency of treatment effect across subgroups?
  - Is it necessary to demonstrate efficacy in subgroups if a treatment effect has been shown in study population?
    - Or to show broadly consistent effects e.g. using forest plots?
  - Is the focus on efficacy or the balance of efficacy and safety?
- Is it to investigate if there is evidence suggesting the treatment effect is inconsistent within the proposed population?
  - What would be the criteria used to conclude the treatment effect is 'inconsistent'?
    - No 'qualitative' inconsistencies?
  - Would some minimal level of efficacy be expected for key subgroups and is there a minimal sample size for subgroups to be meaningful?
  - What is the relevance/importance of the subgroups compared to clinical practice and how patients are treated?

Key clinical considerations - use of subgroup analyses in decision making

- Benefit and risks may not be equally important when assessing subgroups
  - Guideline has little focus on safety endpoints
- When can treatment effects in subgroups be considered ‘sufficient’ to support the product label?
  - Magnitude of point estimates and levels of variability/uncertainty
- Can non pre-specified / exploratory (non-confirmatory) subgroups be used to inform the product label?
  - Taking into account biological rationale and sample size etc
- Credibility of subgroup findings (replication and plausability)
  - What is acceptable?
- Considerations for subgroup analyses in rare diseases / rare events

Priority topic #1: Consistency of subgroup effects

- It is not clear how to define consistency
- It is not clear how to assess consistency
- What statistical methods could be used and what graphical tools are most appropriate/acceptable?
  - Superiority trials vs non-inferiority trials
- What is ‘sufficient’ evidence to conclude consistency has been demonstrated?
  - E.g. pattern of point estimates, develop (new) metric to quantify
  - Will this vary dependent upon the prior support for a subgroup effect?
- What is the role of interaction tests?

Priority topic #2: Defining subgroups

- Use of cut-points to define subgroups
  - Issues of mis-classification or measurement/diagnostic error
  - Agreement of the clinical relevance and utility necessary
- Biological plausibility or external evidence
  - How much evidence is enough and level of detail required?
  - Incorporating new scientific knowledge post design?
- Balancing number of 'important' subgroups and minimising multiplicity issues
- Factors used to define subgroups could be related/dependant
  - Challenges in design and analysis
- When would region in a multi-region clinical trial be an 'important' subgroup?
- What level of information and external evidence would be required to describe the expected (prior) subgroup effects?

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Priority topic #3: ‘Exploratory’ subgroups

- What is the definition of an ‘exploratory’ subgroup and when would a subgroup be considered ‘exploratory’?
- Are subgroups always considered ‘exploratory’ (ICH E9) or could they be considered ‘confirmatory’?
- If all subgroups are exploratory, what is the difference between ‘key subgroups’ and ‘truly exploratory analyses’?
- What are the requirements to assess exploratory subgroups?
  - Necessary to analyse all subgroups noted in section 5.1?
  - Issues with small sample size and number of subgroups

Priority topic #4: Power for subgroups analyses

- Recommend the guideline focuses on the value of assessing subgroups in pooled analyses across multiple trials
  - Reduces (but does not remove) the issue of lack of power when assessing subgroups in individual trials, increases precision to estimate treatment effects
  - Bayesian methods and/or likelihood based approaches could help gain precision
- When would individual trials or pooled analyses need to be powered for 'important' subgroups?
    - It may not be feasible to power for some subgroups
- Guidance on powering for key subgroups in pooled analyses and/or individual trials would be useful

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Other important aspects - planning subgroup analyses (design)

- Limiting number of subgroups and endpoints where subgroups assessed (rank/prioritise)
  - Reduce multiplicity concerns
  - Describe chance of seeing subgroup effect relative to number of analyses
- Stratification is not always necessary or feasible
- Considerations of missing data for subgroup analyses and sensitivity analyses expected
- Are there any specific challenges for subgroups in adaptive designs / adaptive licensing (e.g. timing of subgroup exploration)?
- Assessing subgroups in enrichment (e.g. biomarkers) studies
- Allowing protocol or SAP to be updated when additional subgroups identified during study (before analysis)
- Consulting with regulators on proposed subgroup analyses strategies should be recommended for sponsors

Other important aspects – conducting subgroup analyses

- Potential loss of comparability (lack of balance from randomisation) when assessing subgroups (e.g. when factors are not part of randomisation strata)
- When would results from exploratory analyses call into question interpretation of the overall trial?
- Impact of the scale of endpoints when assessing subgroups and sensitivity analyses expected
- Interpretation of non-linear models, e.g. Cox regression
- When would covariate adjustments be preferable to conducting subgroup analyses?

Other important aspects - interpretation and reporting subgroup analyses

- Limitations of subgroups, potential biases and over-interpretation of results (false positives, false negatives)
  - Lack of power, less precision
  - Cautious interpretation, focus on small number of subgroups
- Is multiplicity a problem if having observed an overall effect, subgroups are ‘exploring’ the treatment effect in the population?
  - Which techniques to use to explore and understand possible effects?
  - Where subgroups help to inform the label, multiplicity is a consideration to avoid incorrectly applying any restrictions/enhancements
- Possible confounding between subgroups / lack of independence
- Replication of subgroup findings and credibility
- Use of graphical tools / presentations to assess treatment effect patterns
  - What patterns would cause concern?

Conclusions

- Important the guideline is clear on what the purpose of subgroup analyses are
  - Defining consistency and measures to flag (in)consistency
- The way in which subgroup analyses are planned, defined, assessed and reported impacts their credibility
  - Prioritisation, biological rationale, statistical model, replication, (in)consistency
- Agreeing subgroup analyses strategies with regulators upfront (before initiating confirmatory trials) is key
  - But with flexibility to incorporate new information
- Sponsors want to understand how subgroups will be used to assess the balance of benefit-risk to inform product label discussions

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