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Subgroups – The quest for enlightenment

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Disclaimer

The views expressed herein represent those of the presenter and do not necessarily represent the views or practices of ICON

Agenda

- PSI Working Group
  - Consensus with Guideline?
- PSI/EFSPI Comments
- Potential topics requiring further clarification

PSI Expert Group

22 April 2010
EMA/CHMP/EWP/117211/2010
Committee for Medicinal Products for Human Use (CHMP)

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

Agreed by Efficacy Working Party	April 2010
Adoption by CHMP for release for consultation	22 April 2010
End of consultation (deadline for comments)	31 July 2010

PSI Working Group – 13th June 2011

- Sarah Bujac (AstraZeneca)
- John Davies (GSK)
- Chrissie Fletcher (Amgen)
- Andrew Garrett (Quintiles)
- Oliver Keene (GSK)
- Alan Phillips (ICON)
- Carol Reid (Roche)
- Stephen Sharp (MRC)

EMA Subgroup Workshop

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 November 2011
EMA/894153/2011
Human Medicines Development and Evaluation

Expert workshop on subgroup analysis

Programme

18 November 2011

PSI Working Group Findings Presented ?

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 January 2014
EMA/CHMP/539146/2013
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the investigation of subgroups in confirmatory clinical trials

DRAFT

Draft Agreed by Biostatistics Working Party	September 2013
Adoption by CHMP for release for consultation	23 January 2014
Start of public consultation	03 February 2014
End of consultation (deadline for comments)	31 July 2014

Comparison vs Guideline

- Pre-agreement with regulatory authorities on important subgroups prior to starting trials
  - Guideline distinguishes between important subgroups, which can be complemented by additional subgroups. These are to be discussed in the protocol. “Key” subgroups, including factors used in the stratification etc. must be planned. There is discussion on “Biological Plausibility”.

- Acknowledge it is difficult to define what is meant by consistency of effect, and the need to balance identification of true effects compared to concluding false positives
  - Guideline discusses consistency in section 4.4 (consistency [homogeneity] of effects in well-defined subgroups) and throughout the guideline.
  - Guideline states on page 13 “There is no widely accepted definition for consistency”!

Comparison vs Guideline

- Acknowledge subgroup analysis does not address within patient differences in effect
  - Discussed in guideline. “It is known that different patients will respond differently to the same intervention” and “same individual may respond differently to the same intervention on different occasions”

- Interaction tests are a possible way of approaching subgroup analyses and should be presented with estimates of size of effect in addition to p-values. Forest plots are useful for visual display, and Bayesian approaches may be potentially useful in some situations
  - Discussed in guideline. Interaction tests, subgroup analyses and Forest plots all needed.

- Need to balance subgroup analysis with regulatory burden

Executive Summary – Other Points

- Subgroup analysis is a very difficult area
- Replication across two trials can help with interpretation ✓
  - Guideline addresses replication, and provide clear guidance regarding expectations.
- Region is a subgroup, but hard to interpret biologically ✓
  - Section 5.3 recommends including country or region and provides explanation behind this.
- Analysis should depend on how heterogeneous the target population is ✓
  - Addressed in guideline.
- Scale of measurement is important- absolute vs. relative ✓
  - Discussed page 8.
- Increased focus and discussion on subgroups at design stage ✓
    - Discussed in the context of “key” and exploratory subgroups.
- Subgroup characteristics should be easy to measure ✓
  - Discussed in terms of plausibility and in context of scenario 2 …….. “A pharmacological rationale, or a mechanistically plausible explanation……”

- Good Guideline
- Consensus with PSI Working Group

PSI/EFSPI Comments

- Initial set PSI/EFSPI comments comprised 35 pages
- Final version
  - 6 major comments
  - 15 pages of specific comments on text
- Not what I was expecting!
- EFPIA comments comprised 48 pages
- Potential opportunities for improvement

Suggestions

1. Consistency/homogeneity versus inconsistency/heterogeneity – which is the focus and how does this differ when considering superiority versus non-inferiority "trials"?
    - Sponsors assume homogeneity
    - Regulators seem to assume heterogeneity and burden of proof is with sponsor to establish an effect in each subgroup
    - Discuss in more detail in "Introduction and Problem Statement" sections

2. Should the sub group guideline be focused on "Integrated Analyses" rather than study level?
    - Focus seems to be single pivotal trial
    - Discuss in more detail the limitations of subgroups
        - For example, small sample sizes, Rare diseases

3. Definition of consistency
    - Acknowledge it is difficult to define what is meant by consistency of effect, and the need to balance identification of true effects compared to concluding false positives
    - What evidence is needed to conclude consistency has been demonstrated?
        - Crux of the issue
    - Global round table workshop/scientific meeting on this topic?

Suggestions

4. Subgroups for reimbursement
    - How should these be handled…….. Biologically plausible or exploratory?
    - PSI/ESFPI comment – include general classification of subgroup analysis approaches
        - Confirmatory Subgroups for label claims
        - Key Exploratory subgroups – where there is a rationale or a plausible explanation worthy of investigation
        - Truly Exploratory subgroups – which would require an extreme effect or replication for credibility.

5. Use of subgroups in adaptive designs
    - Is there a difference in the Adaptive design setting?

6. Dose adjustment for different subgroups… and the impact on benefit/risk

Summary

But we can make it better

So the quest continues!