Session 302, JSM 2013: Key Subgroup Analysis Issues in Clinical Trials, Discussion

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Overview of Subgroup Identification Approaches in Clinical Research

• Principles and standards for subgroup analysis in clinical research

• Data mining approaches for subgroup identification

• SIDES Method

Applications:

> Prospective identification/validation of biomarkers/subgroups;
> Evaluation of data prior to Phase 3 trials to identify possible population for enrichment.
Alexei Dmitrienko, Confirmatory subgroup analysis: Multiple testing approaches

• Clinical trials with pre-specified subpopulation
  ➢ Enhanced efficacy in sub-population
  ➢ Both overall population and sub-populations are important
  ➢ Efficacy at least in one population

• Multiplicity adjustments to control overall Type I error
  ➢ Control of familywise error rate
  ➢ Account for logical relationships and utilize available distribution information
  ➢ $\alpha$ allocation and propagation
  ➢ Optimality criteria
Brian Millen,
Decisionmaking in Confirmatory Multipopulation Tailoring Clinical Trials

- Clinical trials with pre-specified subpopulation
  - Enhanced efficacy in subpopulation
  - Biomarker-positive and biomarker-negative subpopulations
- Multiple testing
- Influence condition
- Interaction condition
- Frequentist and Bayesian approaches
Additional Information and Thoughts

- EMA/286914/2012: “Concept paper on the need for a guideline on multiplicity issues in clinical trials”, 2012
- EMA/CHMP/EWP/117211/2010: ”Concept paper on the need for a Guideline on the use of Subgroup Analyses in Randomised Controlled Trials”, 2010

-Draft FDA guidance: ”Guidance for Industry: Analysis of Clinical Trials with Multiple Endpoints”, expected to be released soon
• Criteria for Multiple Testing
  > **Strong control** of type I error rate
  > Optimize power by accounting for logical relationships & correlations

• Recent Development in Multiple Testing Strategies
  > Linear hierarchical structure
    - Sequential Testing
      Reference: Dmitrienko, Tamhane and Wiens (2008)
    - Sequential Testing with Retesting
      Reference: Dmitrienko, Kordzakhia, Tamhane (2011)
    - Sequential Testing with Multiple Retesting

  > Symmetric Hierarchical structure
    - Simultaneous testing for two families
    - Simultaneous testing for multiple families
      Reference: Kordzakhia, Dmitrienko (2012)
Additional Information and Thoughts (Cont.)

- Biomarker-driven designs to facilitate precision medicine/ find sub-populations with enhanced benefit from treatment/ tailoring treatment
  - Biomarker discovery/ selection & validation designs
  - Biomarker stratified & strategy designs
  - Population enrichment (standard and adaptive designs)

- FDA Draft Guidance (December, 2012): Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products

Quantifying success in stratified medicine


Sub-population selection based on a short-term endpoint


Applications

Additional References (Cont.)

Adaptive Population Enrichment design combining two stages using flexible p-value combination tests with the closed testing principle


Approaches to constructing multiplicity adjustment procedures with multiple patient populations

Additional References (Cont.)

Miscellaneous