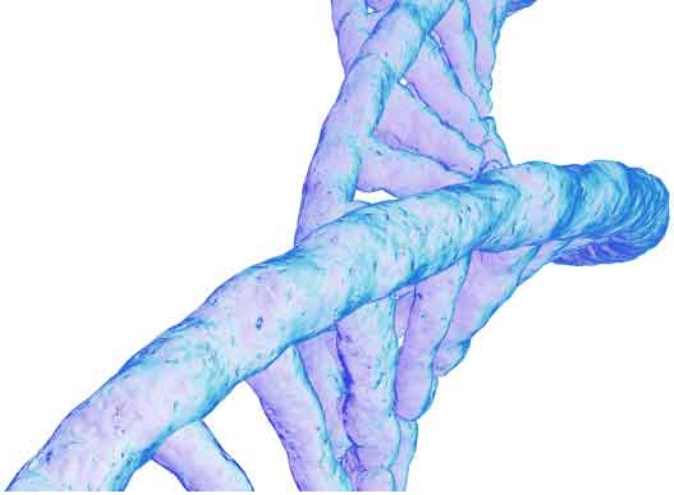

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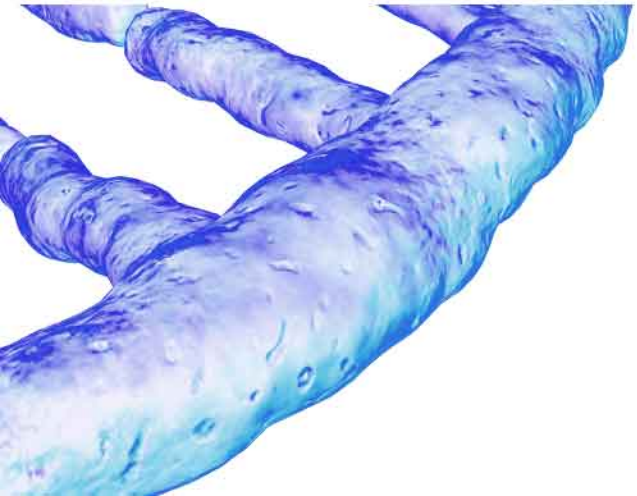
Navigating the new health

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

Olga Marchenko
CSDD, Innovation



Ilya Lipkovich, Overview of Subgroup Identification Approaches in Clinical Research

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- 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

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- Clinical trials with pre-specified subpopulation
  - Enhanced efficacy in sub-population
  - Both overall population and subpopulations 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
  - ά allocation and propagation
  - Optimality criteria

Brian Millen, Decisionmaking in Confirmatory Multipopulation Tailoring Clinical Trials

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- 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
- CPMP/ICH/363/96: “ICH E9 Statistical Principles for Clinical Trials”, 1998
- CPMP/EWP/908/99: “Points to Consider on Multiplicity Issues in Clinical Trials”, 2002
- CHMP/EWP/2459/02: “Reflection Paper on Methodological Issues in Confirmatory Clinical Trials planned with an adaptive design”, 2007

- **Draft FDA guidance: ”***Guidance for Industry: Analysis of Clinical Trials with Multiple Endpoints”,* expected to be released soon

Additional Information and Thoughts (Cont.)

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- 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

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf

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Applications

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Additional References (Cont.)

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