Multiplicity Guidelines

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Regulatory Guidelines

Regulatory guidelines

FDA guideline

Draft guidance on multiplicity issues in clinical trials (2017)

EMA guideline

Draft guideline on multiplicity issues in clinical trials (2017)

Revision of *Points to consider on multiplicity issues in clinical trials* (2002)

Regulatory guidelines

FDA guideline

Provides information on key principles and underlying methodology

EMA guideline

Focuses on general principles

Overview of the FDA Guideline

FDA guideline's scope

Section II

In the following sections, the issues of multiple endpoints and methods to address them are illustrated with examples of different study endpoints. Both the issues and methods that apply to multiple endpoints also apply to other sources of multiplicity, including multiple doses, time points, or study population subgroups.

Key topics

Type I error rate

Clear definition of Type I error rate control in confirmatory trials

General settings

Traditional setting (single source of multiplicity) and advanced setting (several sources of multiplicity)

Success criteria (win criteria)

Commonly used success criteria, e.g., at least one objective is met or all objectives are met

Key topics

Analysis of hierarchically ordered endpoints

Type I error rate control for primary and secondary endpoints (or, more generally, ordered clinical objectives)

Commonly used multiple testing procedure

Comprehensive summary of procedures used in traditional settings and advanced settings (gatekeeping strategies)

Key topics

Analytical approach

Fundamental facts such as the importance of an analytical approach to deriving valid multiplicity adjustments (simulation-based approaches are not appropriate)

Power evaluations

Simulation-based evaluations to support power and sample size calculations

Topics not covered

Multiplicity in early-stage trials

Dose-finding strategies, use of global tests, etc

Multiplicity in exploratory settings

Analysis of safety endpoints, post-hoc subgroup analysis, etc

Multiplicity issues in adaptive trials

See *Adaptive Design Clinical Trials for Drugs and Biologics*

Review papers

Recent review papers and tutorials

Dmitrienko, D'Agostino and Huque. (2013). Key multiplicity issues in clinical drug development.

Dmitrienko and D'Agostino. (2013). Tutorial in Biostatistics: Traditional multiplicity adjustment methods in clinical trials.

Alosh, Bretz and Huque (2014). Advanced multiplicity adjustment methods in clinical trials.

Response to the FDA Guideline

Communication channels and forums

Statistics in Medicine

Commentaries on FDA and EMA multiplicity guidelines (to be published in 2017)

Journal of Biopharmaceutical Statistics

Special issue on multiplicity issues in clinical trials (to be published in early 2018)

Contributions from regulatory agencies, industry and academia (US, Europe and Japan)

Communication channels and forums

Regulatory-Industry Statistics Workshop 2017

Session: Multiplicity Issues in Clinical Drug Development

Speakers: Lisa LaVange (FDA), Ralph D'Agostino (Boston University), Alex Dmitrienko (Mediana Inc)

ASA Biopharmaceutical Section

Online training program: Key Multiplicity Issues in Clinical Trials

http://sprmm.com/asa-biopharmaceutical-section/

Summary

Summary

FDA guideline

Information and recommendations presented in the FDA guideline will encourage drug developers to learn more about novel approaches to performing multiplicity adjustments and judiciously apply them in confirmatory clinical trials

References

References

Alosh, M., Bretz, F., Huque, M. (2014). Advanced multiplicity adjustment methods in clinical trials. *Statistics in Medicine*. 33, 693-713.

Dmitrienko, A., D'Agostino, R.B., Huque, M.F. (2013). Key multiplicity issues in clinical drug development. *Statistics in Medicine*. 32, 10791111.

Dmitrienko, A., D'Agostino, R.B. (2013). Tutorial in Biostatistics: Traditional multiplicity adjustment methods in clinical trials. *Statistics in Medicine*. 32, 5172-5218.