Analysis of Clinical Trials with Multiple Objectives

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Outline

Regulatory guidelines

FDA and EMA draft guidance documents

Multiplicity problems in clinical trials

Selection of multiple testing methods

Multiplicity problems in adaptive trials

Regulatory Guidelines

Regulatory guidelines

FDA guidance

Draft guidance on multiplicity issues in clinical trials (2017)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 guidance

Provides information on key principles and underlying methodology

EMA guideline

Focuses on general principles

Overview of the FDA Guidance

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

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

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 Guidance

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

Biopharmaceutical Section

Online training program: Key Multiplicity Issues in Clinical Trials

Convenient and inexpensive training options for the Section's members

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

Selection of Multiple Testing Methods

Multiple testing methods

Selection of most appropriate methods

Numerous multiple testing methods have been developed

Need guidelines that facilitate the selection of most appropriate methods for a given trial

"Statistical methods and approaches that have been suggested in the literature in recent years now deserve to be digested and placed in the context of how they can be best used in clinical trials" (O'Neill, 2006)

Case study

APEX trial

Phase III clinical trial for prevention of venous thromboembolism (VTE) (Cohen et al., 2016)

Trial design

Novel treatment (betrixaban) versus control

Primary endpoint

Composite binary endpoint based on deep-vein thrombosis, nonfatal pulmonary embolism or VTE-related death at Day 35

APEX trial

Key biomarkers

D-dimer level at baseline

Patent's age

Three pre-defined patients populations

Subpopulation 2 (elevated D-dimer)

Subpopulation 1 (elevated D-dimer or older than 75 years)

Overall population

APEX trial

Trial results

Treatment effect within the three patients population was evaluated using the fixed-sequence test

Treatment effect in Subpopulation 2 was not significant and the other two populations could not be tested

Alternative strategies

How would other multiple testing methods perform in this trial?

Clinical scenario evaluation

General framework

Clinical scenario evaluation (CSE) approach was developed in Benda et al. (2010) and other publications

Motivation

CSE approach encourages clinical trial researchers to employ systematic and quantitative approaches to evaluating candidate trial designs and analysis methods to enable better decision making

Clinical trial optimization

Clinical scenario evaluation

An important application of the CSE framework is clinical trial optimization

General theme

Utilize CSE to transition from traditionally used approaches to optimal approaches to selecting trial designs and analysis strategies

Inform decision making at different stages of a drug development program to maximize the overall probability of success

Clinical trial optimization

Publications

Review of general approaches to clinical trial optimization (*Clinical Trial Optimization Using R* edited by Dmitrienko and Pulkstenis, 2017)

Examples

Optimal selection of multiplicity adjustments in Phase III trials, e.g., selection of most efficient and robust multiple testing procedures, optimal selection of procedure parameters, etc

Multiplicity Issues in Adaptive Trials

Adaptive trials with multiple objectives

Multivariate objectives

Phase III trials with data-driven decision rules (group-sequential and adaptive trials) and several sources of multiplicity (e.g., several dose-control comparisons, several endpoints, etc)

Regulatory guidelines

Adaptive design clinical trials for drugs and biologics (FDA, 2010)

Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design (EMA, 2007)

COMPASS trial

Trial information

Evaluate the efficacy and safety of rivaroxaban alone or in combination with aspirin in patients with stable atherosclerotic vascular disease (Eikelboom et al., 2017)

Three sources of multiplicity

Two dose-control comparisons

Three decision points

Four endpoints (one primary and three secondary endpoints)

Adaptive trials with multiple objectives

Multi-stage design

Split the trial into multiple stages (e.g., before and after an interim analysis)

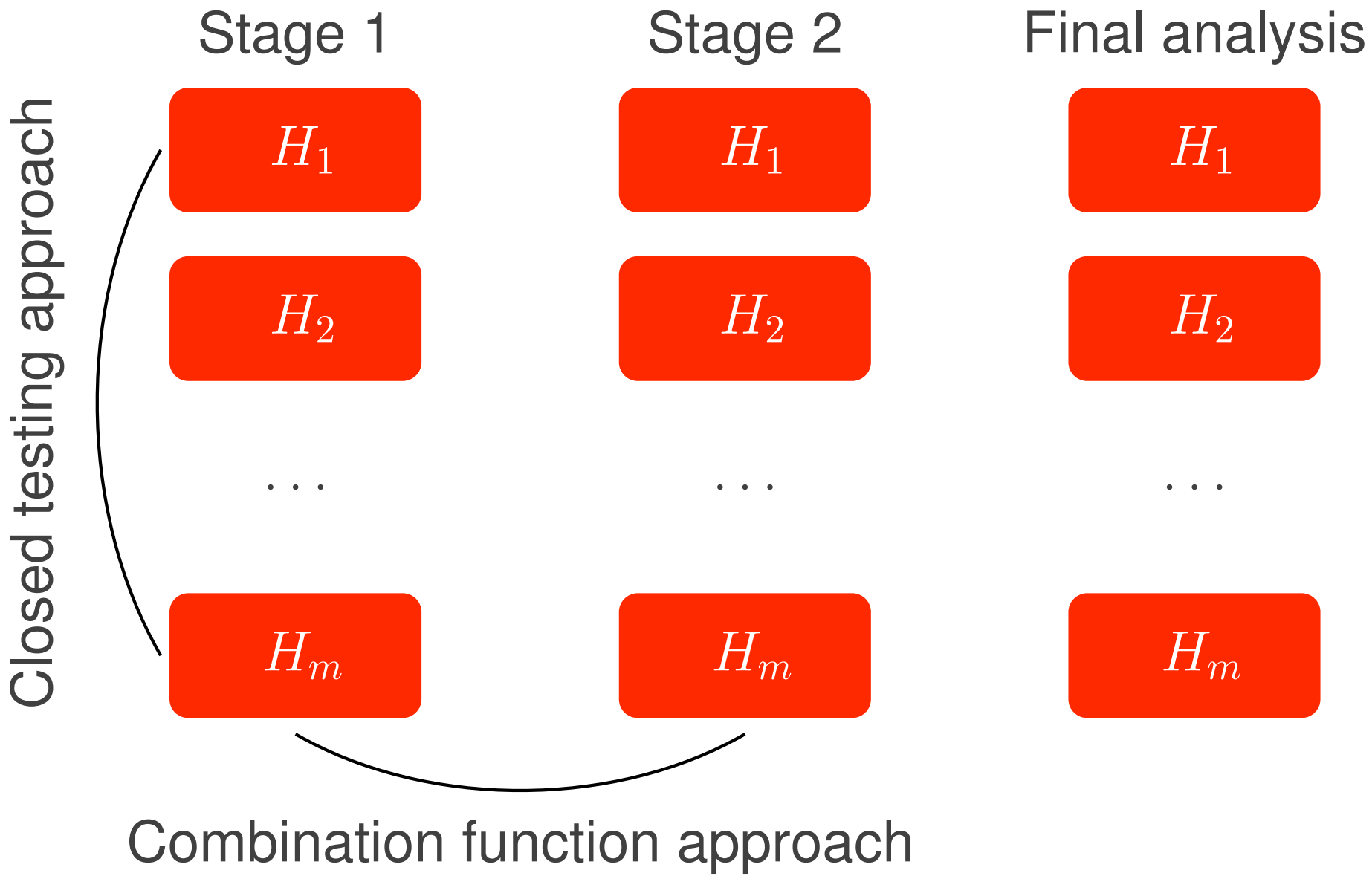
Closed testing approach

Define a multiple testing procedure within each stage

Combination function approach

Combine multiplicity-adjusted inferences across the stages

Adaptive trials with multiple objectives



Adaptive trials with multiple objectives

Flexible decision rules

Lower significance level for the primary endpoint and higher significance levels for the secondary endpoints at early interim looks

Example

Adjusted significance levels at the first interim analysis

Primary endpoint is tested at 0.0001

Secondary endpoints are tested at 0.002

Adaptive trials with multiple objectives

Recent publications

Chain procedures/graphical procedures in group-sequential and general adaptive trials (Maurer and Bretz, 2013; Sugitani, Bretz and Maurer, 2016)

More powerful gatekeeping procedures (e.g., Hommel-based gatekeeping procedures) in adaptive trials (Kordzakhia, Dmitrienko and Ishida, 2018)

Summary

Summary

Multiplicity issues in clinical trials

Multiplicity adjustments are required by regulatory agencies in Phase III trials with multiple objectives

FDA and EMA guidelines

Encourage drug developers to learn more about novel approaches to multiplicity adjustments and to judiciously apply them in confirmatory clinical trials

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