Branching tests in clinical trials with multiple objectives

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Outline

Gatekeeping procedures

Serial and parallel testing

Branching procedures

Multiple tests for clinical trials with hierarchically ordered objectives

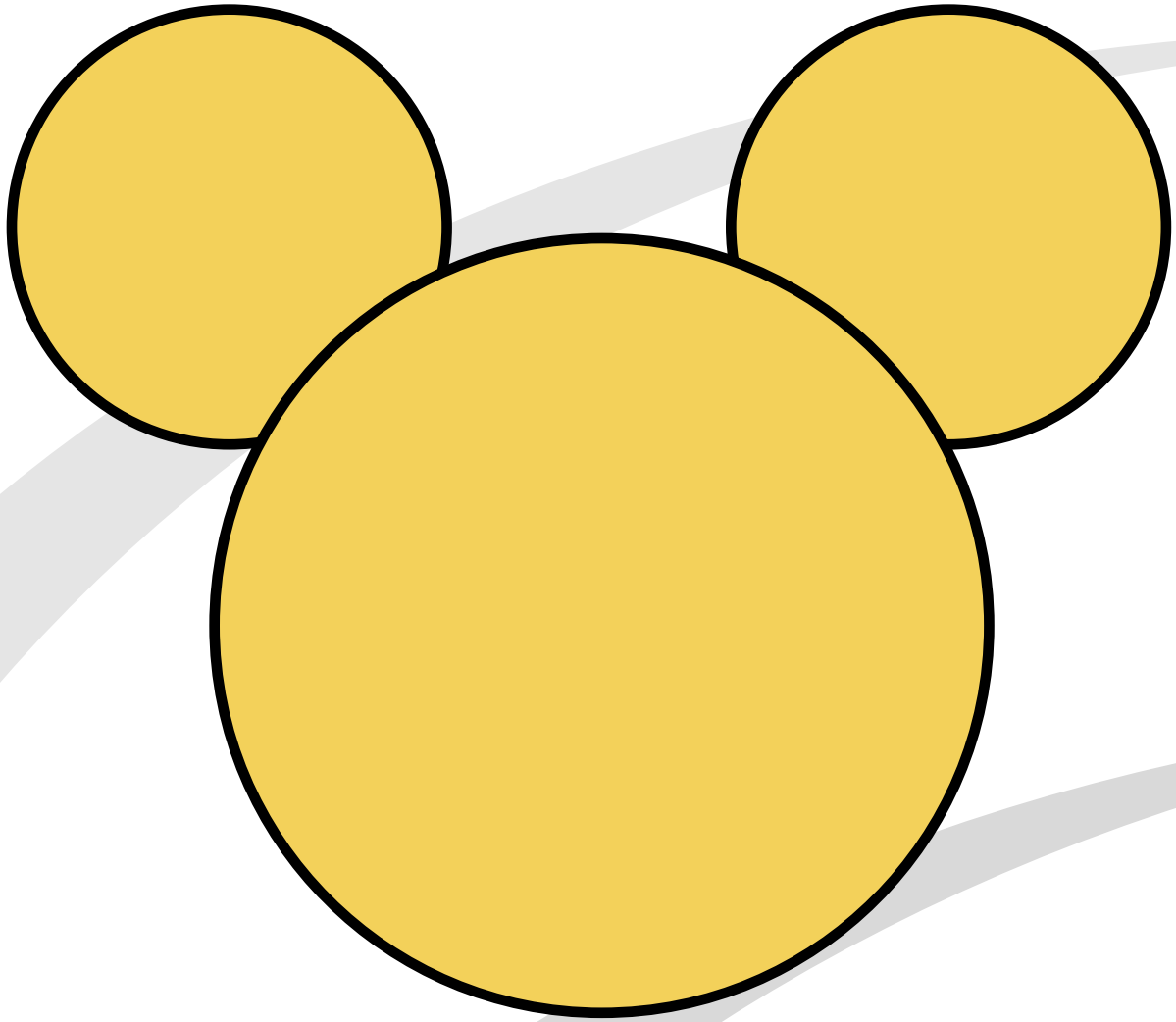
Extension of gatekeeping methods

Clinical trial examples

Trial with multiple endpoints and objectives

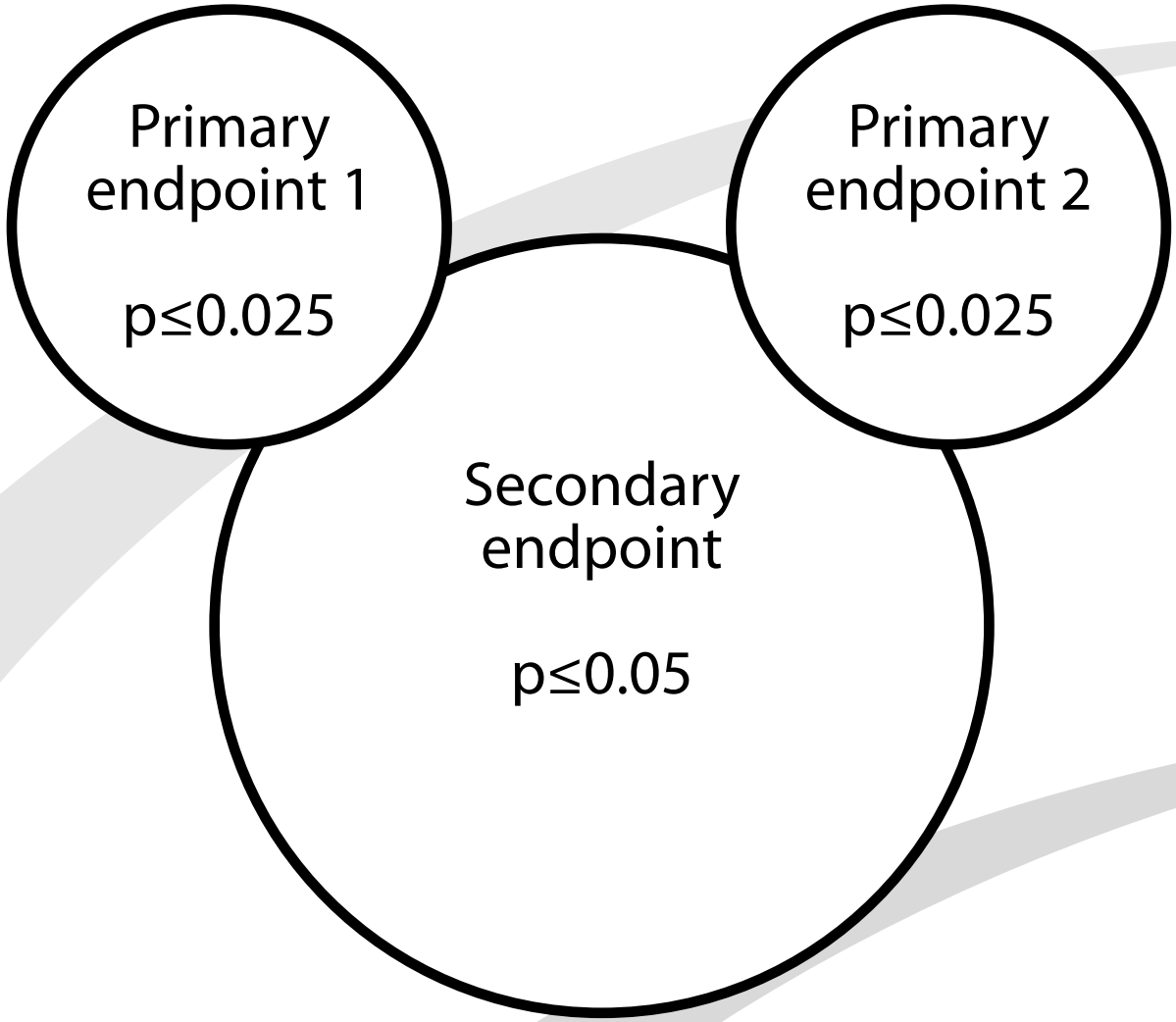
Dose-finding trial with multiple endpoints

Mickey Mouse problem



Multiple endpoints

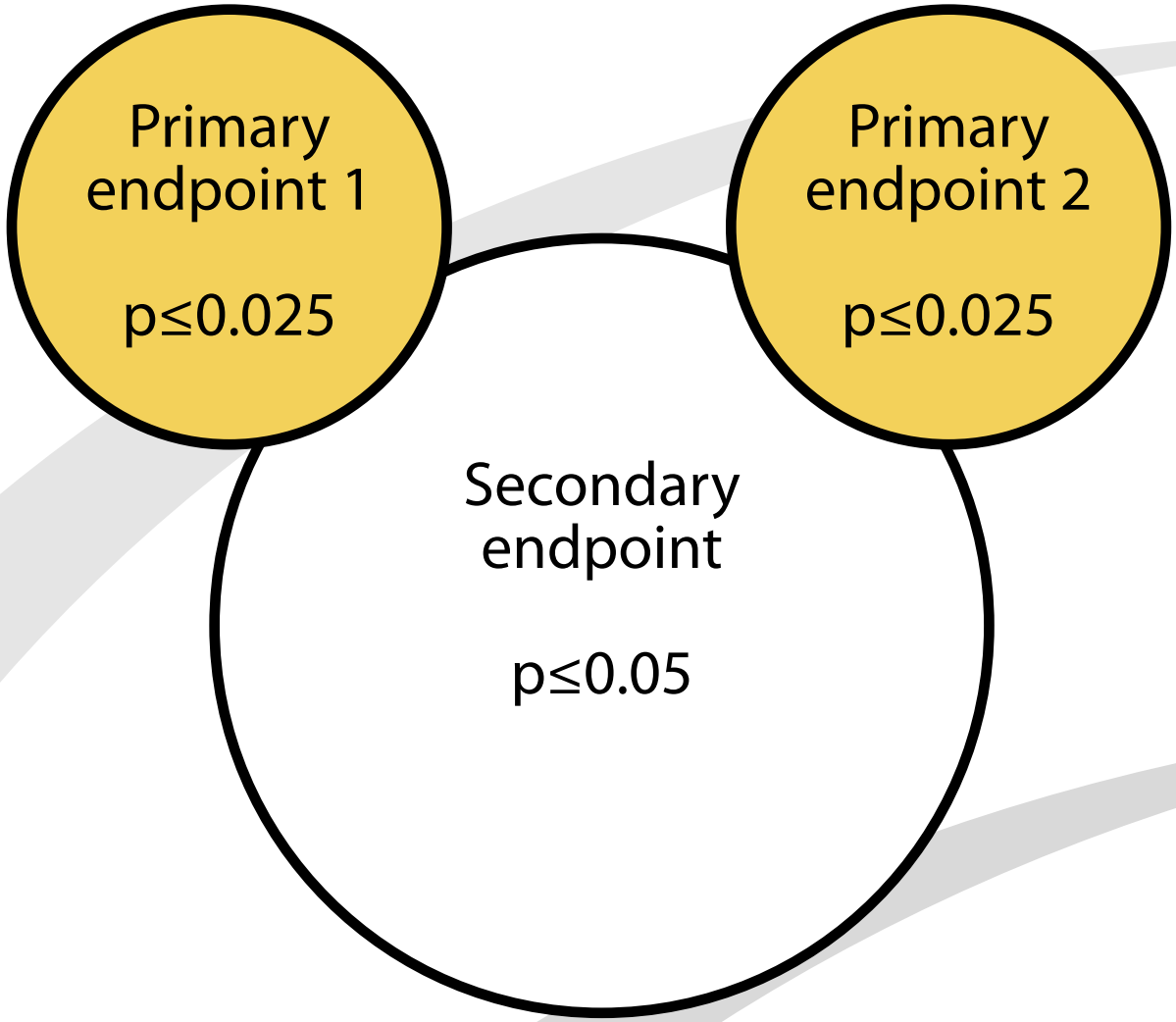
Two co-primaries/one secondary



Multiple endpoints

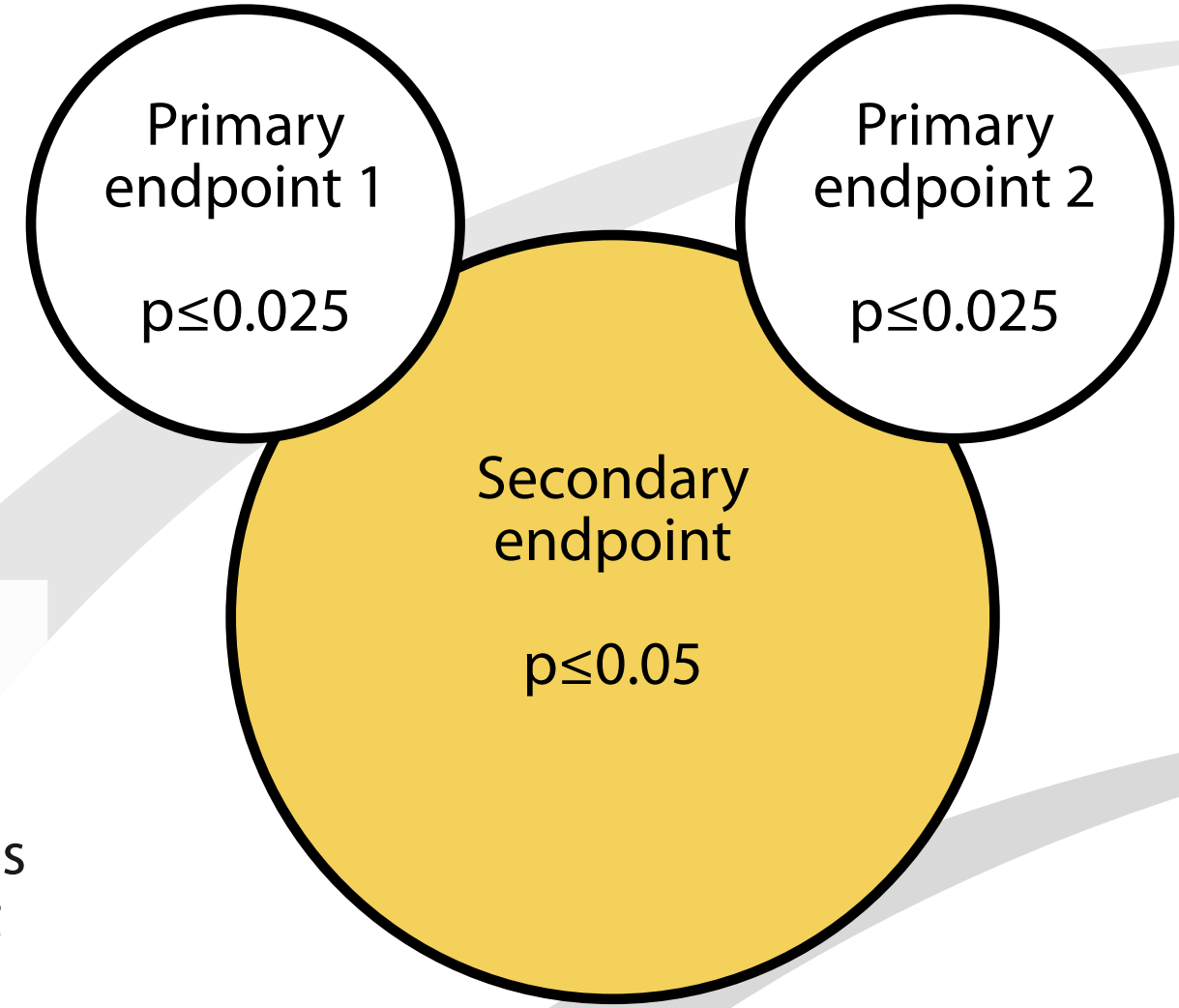
Two co-primaries/one secondary

Family 1: Bonferroni test



Multiple endpoints

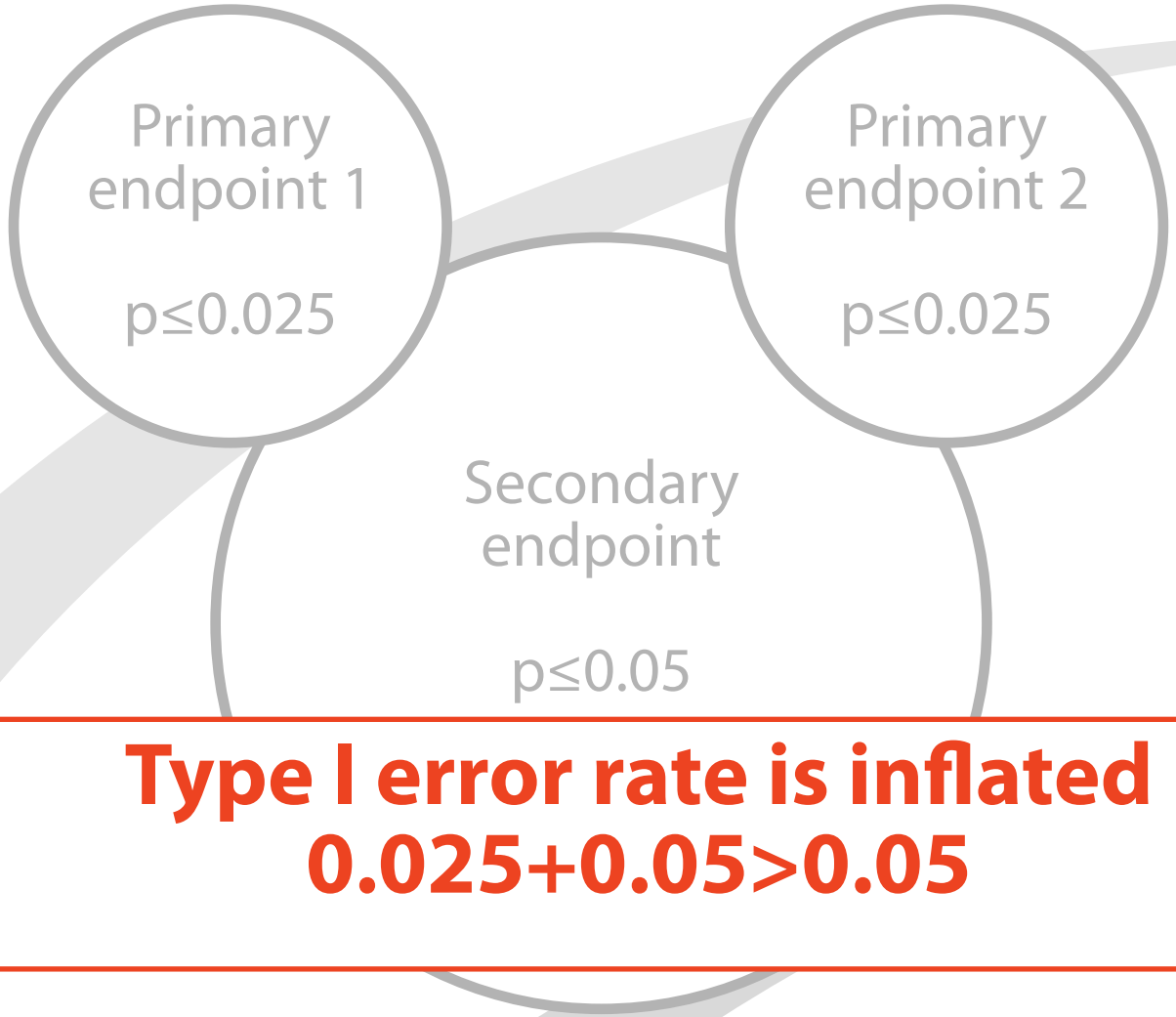
Two co-primaries/one secondary



Family 2: Test if at least one primary endpoint is significant

Multiple endpoints

Two co-primaries/one secondary



Type I error rate is inflated
0.025+0.05>0.05

Gatekeeping methods

Gatekeeping procedures

Multiple testing procedures for sequential families of null hypotheses

Serial gatekeeping methods, Westfall and Krishen (2001)

Parallel gatekeeping methods, Dmitrienko, Offen and Westfall (2003)

Parallel gatekeeping methods with logical restrictions, Chen, Luo and Capizzi (2005)

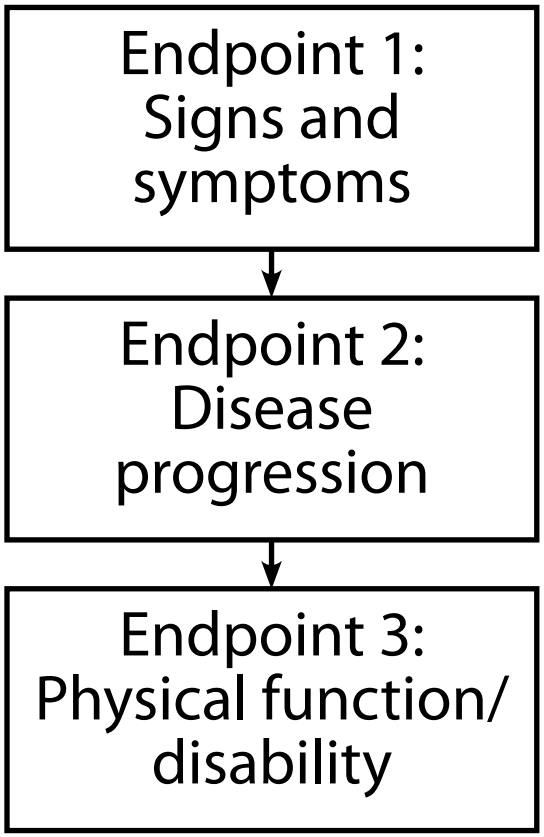
General overview

Dmitrienko et al (2005, Chapter 2)

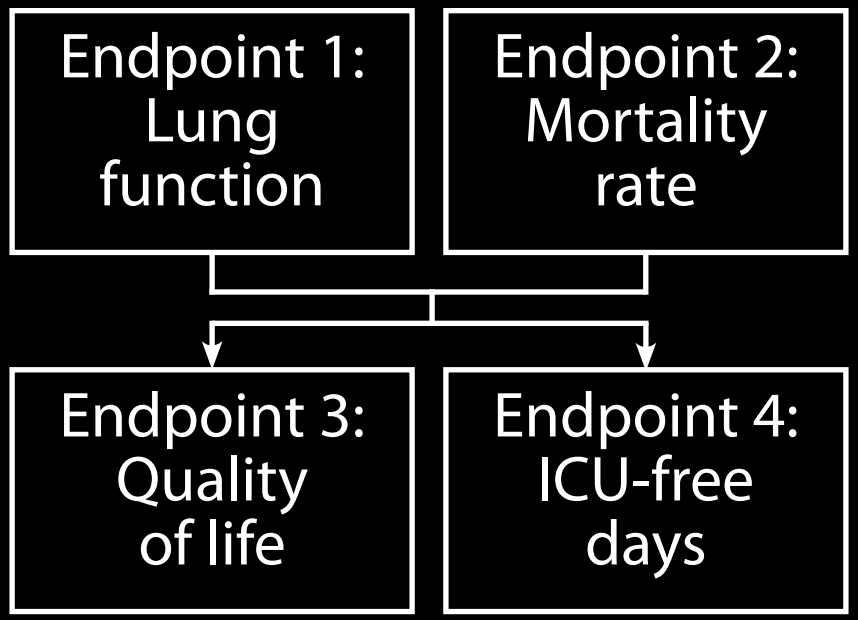
Gatekeeping methods

Serial versus parallel strategies

Serial strategy
(Rheum arthritis)



Parallel strategy
(Acute lung injury)



Branching methods

Extension of gatekeeping methods

trategy
arthritis)

oint 1:
s and
toms

oint 2:
ease
ession

oint 3:
function/
bility

Branching methods

Trial designs are becoming increasingly more complex

Clinical researchers explore complex testing strategies

Examples

Two- or three-dimensional rather than simple sequential strategies

Logical restrictions

Parallel
(Acute lu

Endpoint 1:
Lung
function

Endpoint 3:
Quality
of life

Clinical trial examples

Hypertension trial

Design

Experimental drug versus active control

Four endpoints

Primary (P): Systolic blood pressure

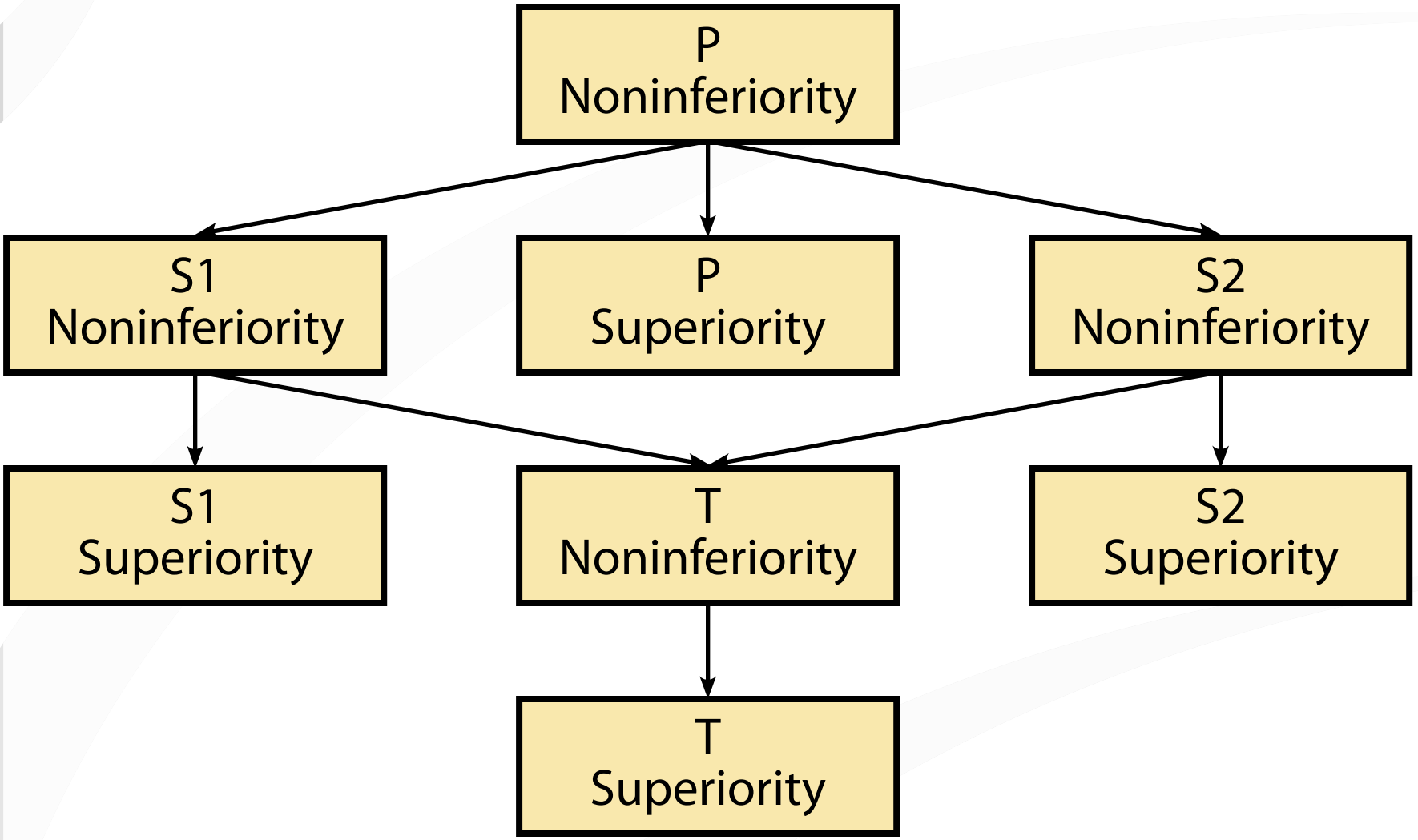
Secondary (S1 and S2): Diastolic blood pressure and proportion of patients with controlled systolic/diastolic blood pressure

Tertiary (T): Average blood pressure based on ambulatory blood pressure monitoring

Noninferiority vs superiority

Hypertension trial

Decision tree



P=Primary, S1 and S2=Secondary, T=Tertiary endpoints [Slide 12]

Clinical trial examples

Type II diabetes trial

Design

Three doses (L, M and H) versus placebo (P)

Three endpoints

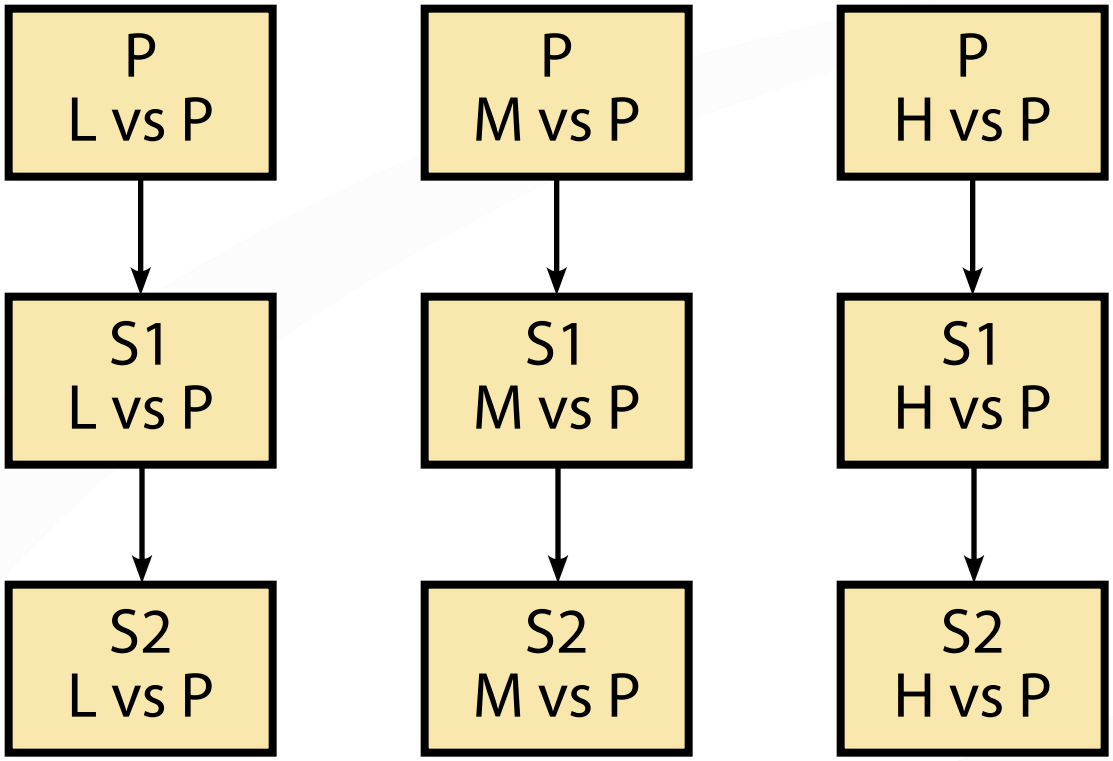
Primary (P): Hemoglobin A1c

Secondary (S1 and S2): Fasting serum glucose and HDL cholesterol

Logical restrictions

Diabetes trial

Decision tree



P=Primary, S1 and S2=Secondary endpoints

Branching framework

Closed testing principle

Marcus, Peritz and Gabriel (1976)

Define a branching procedure based on Bonferroni test

Compute multiplicity-adjusted p-values

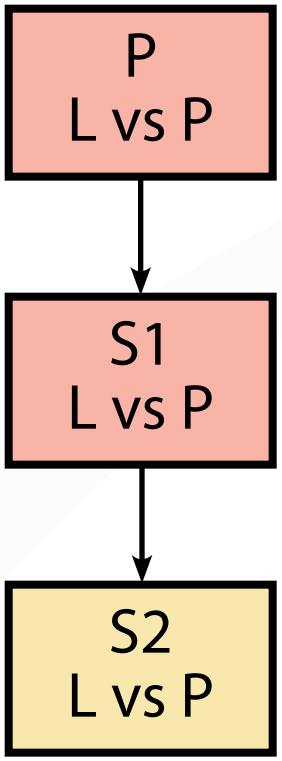
Gatekeeping sets

Gatekeeping sets

Gatekeepers specific to each null hypothesis

Parallel gatekeeping and serial gatekeeping sets for each null hypothesis

Serial gatekeeping set



P
M vs P

P
H vs P

Null hypothesis H

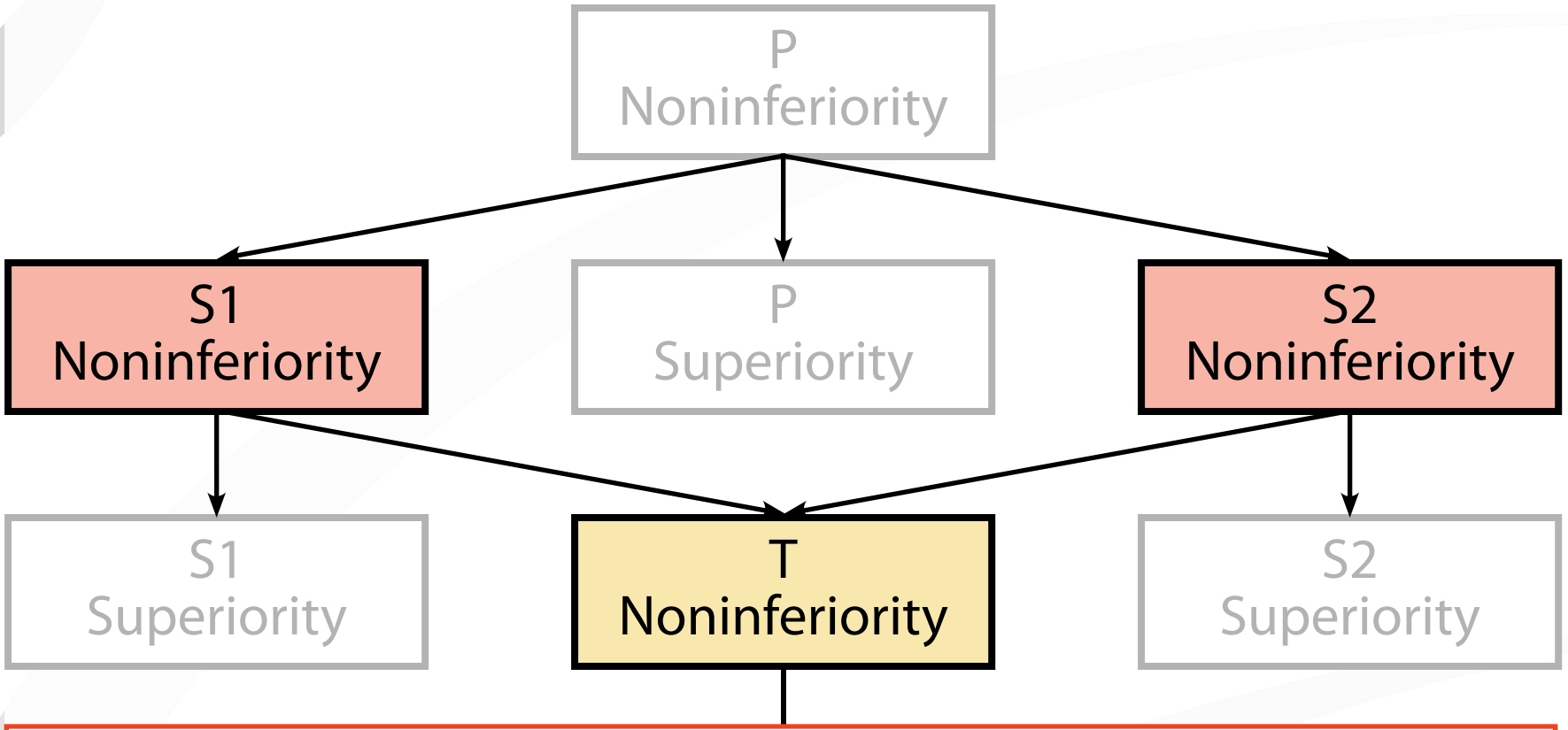
Serial gatekeeping set:

All null hypotheses must be rejected in this set to test H

M vs P

H vs P

Parallel gatekeeping set

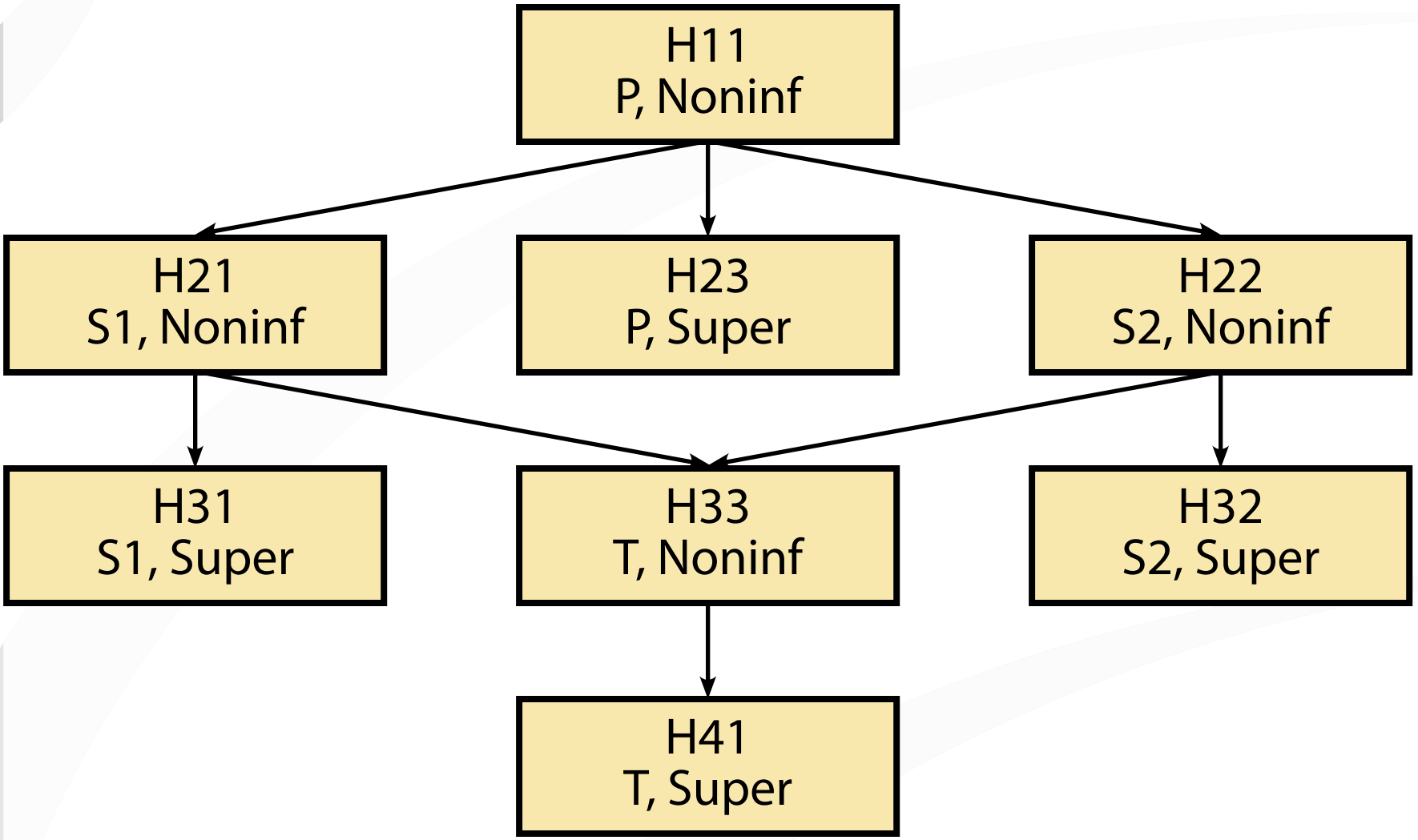


Parallel gatekeeping set for H:

At least one null hypothesis must be rejected in this set to test H

Hypertension trial

Decision tree



Hypertension trial

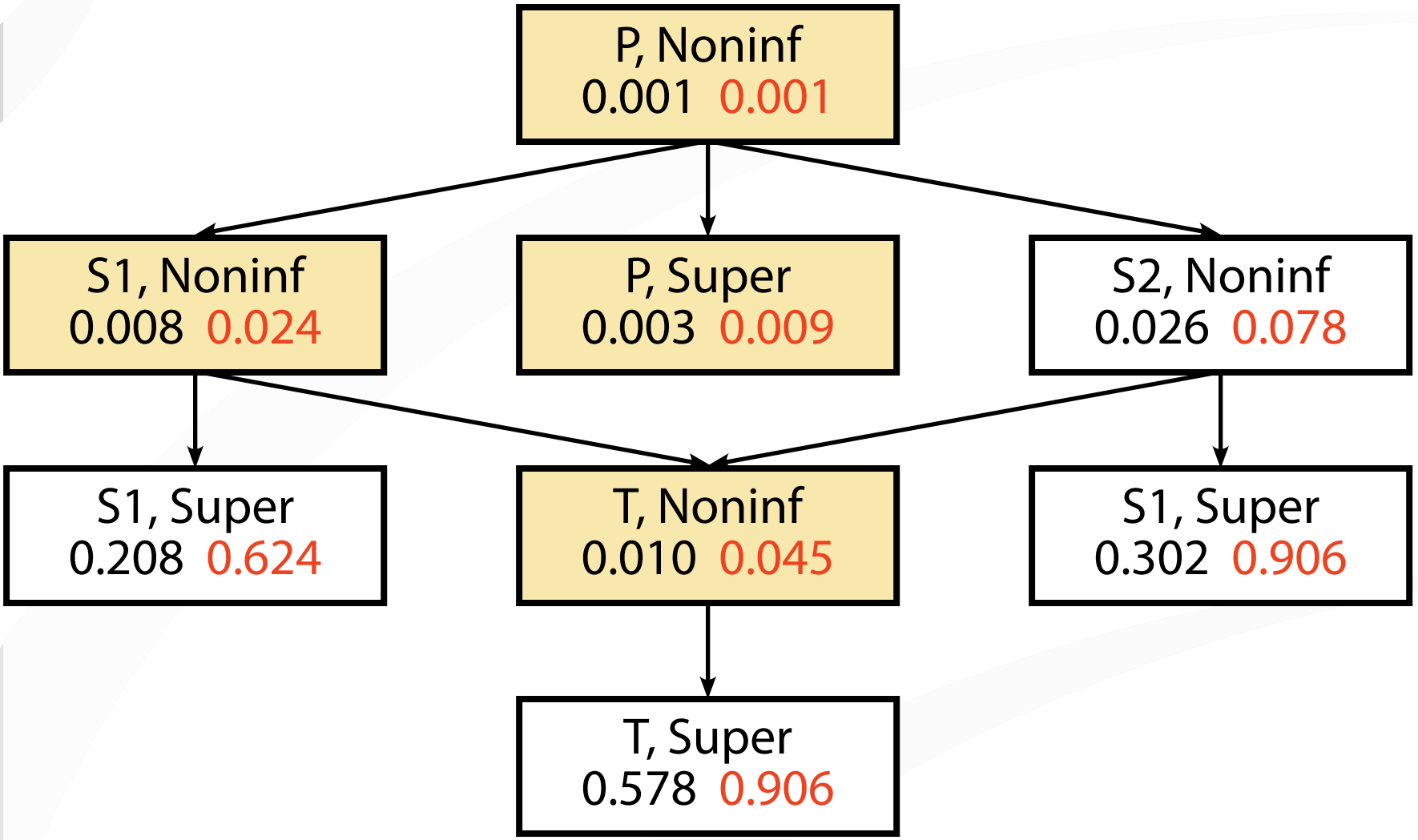
Parallel gatekeeping sets

Null hypothesis	Parallel set
H11 (P, Noninf)	NA
H21 (S1, Noninf)	H11
H22 (S2, Noninf)	H11
H23 (P, Super)	H11
H31 (S1, Super)	H21
H32 (S2, Super)	H22
H33 (T, Noninf)	H21, H22
H41 (T, Super)	H33

Serial gatekeeping sets are empty

Hypertension trial

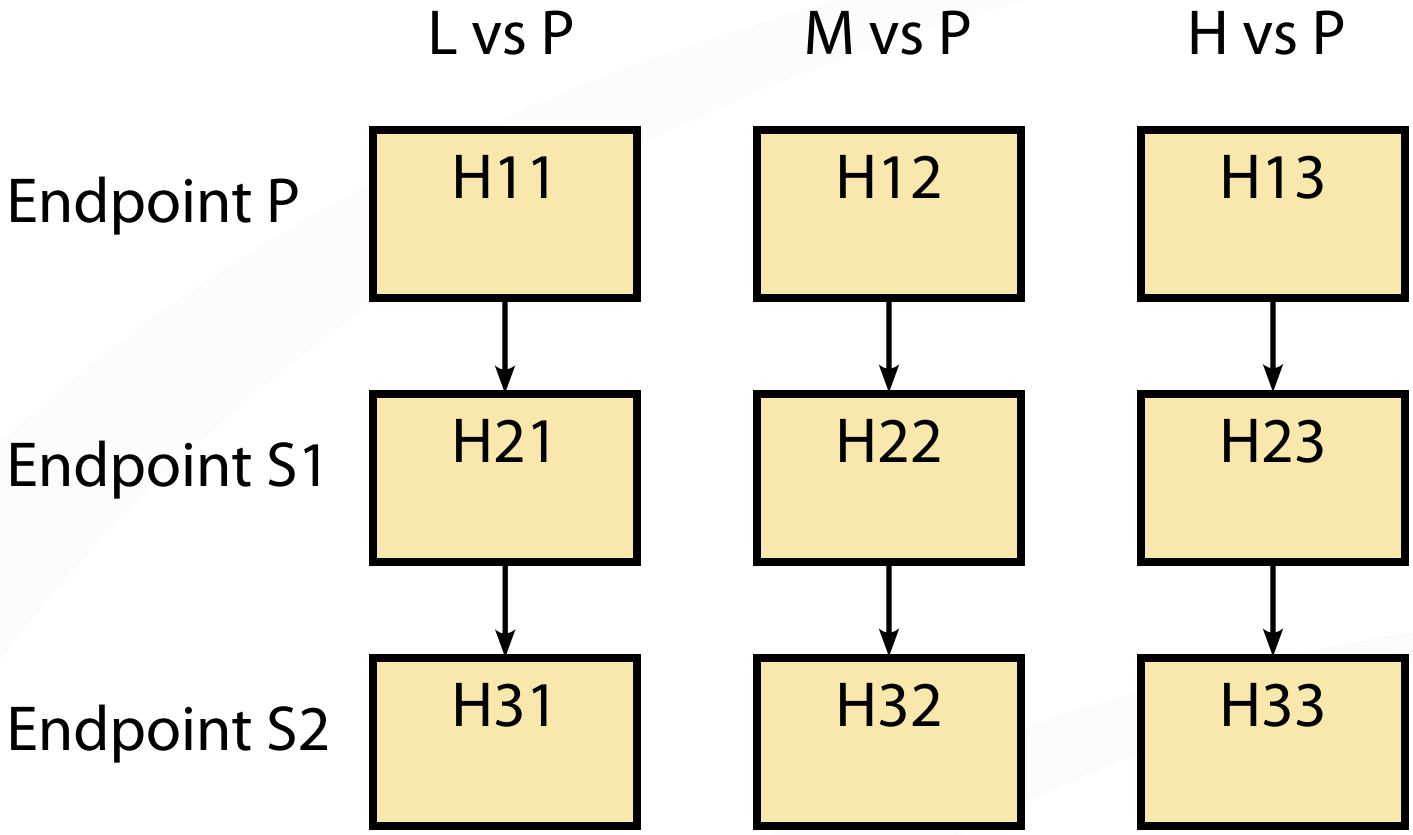
Multiplicity-adjusted p-values



Raw p-values Multiplicity-adjusted p-values

Diabetes trial

Decision tree



Diabetes trial

Serial gatekeeping sets

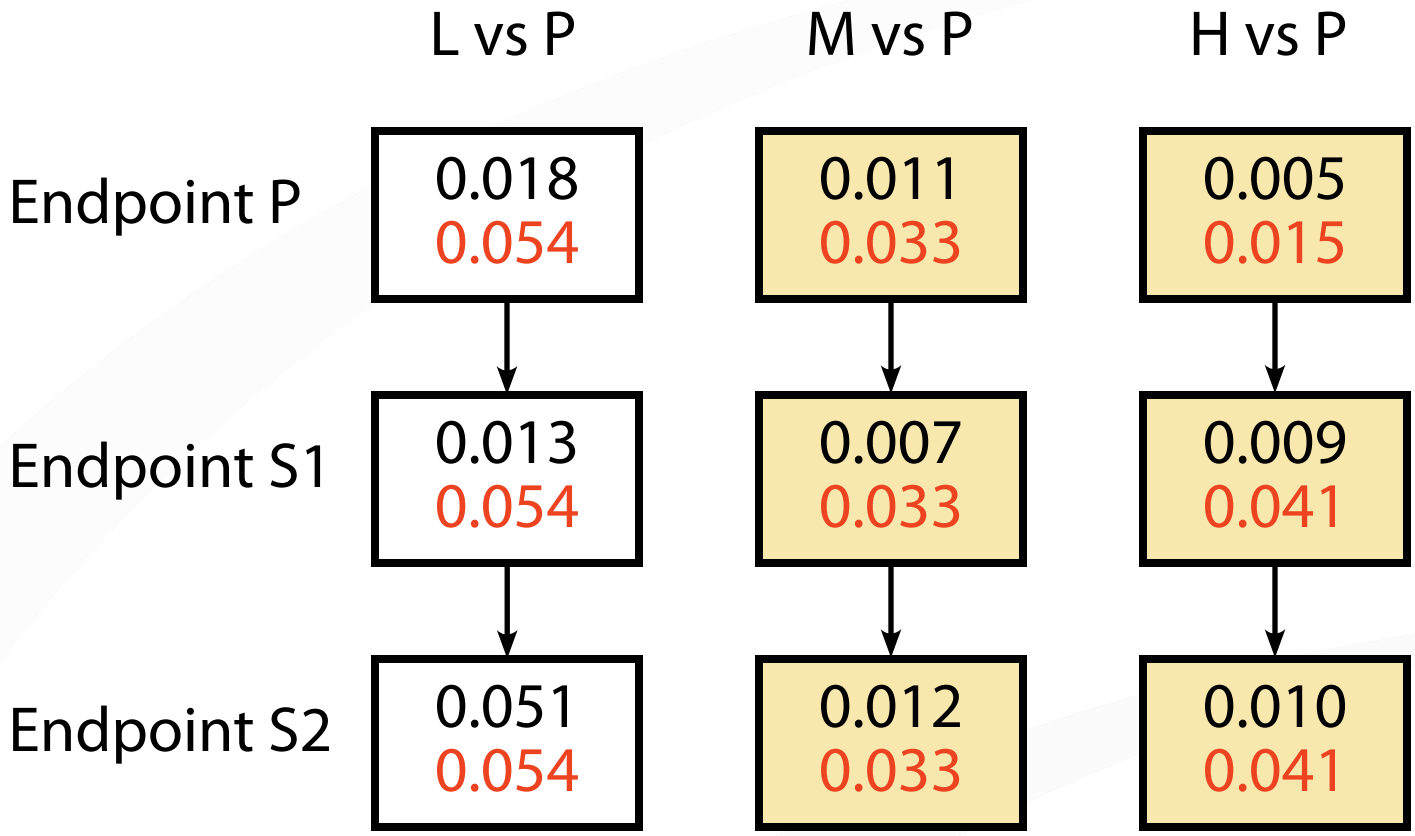
Null hypothesis	Serial set
H11 (P, L vs P)	NA
H12 (P, M vs P)	NA
H13 (P, H vs P)	NA
H21 (S1, L vs P)	H11
H22 (S1, M vs P)	H12
H23 (S1, H vs P)	H13
H31 (S2, L vs P)	H11, H21
H32 (S2, M vs P)	H12, H22
H33 (S2, H vs P)	H13, H23

Parallel gatekeeping sets are empty

Diabetes trial

Branching strategy

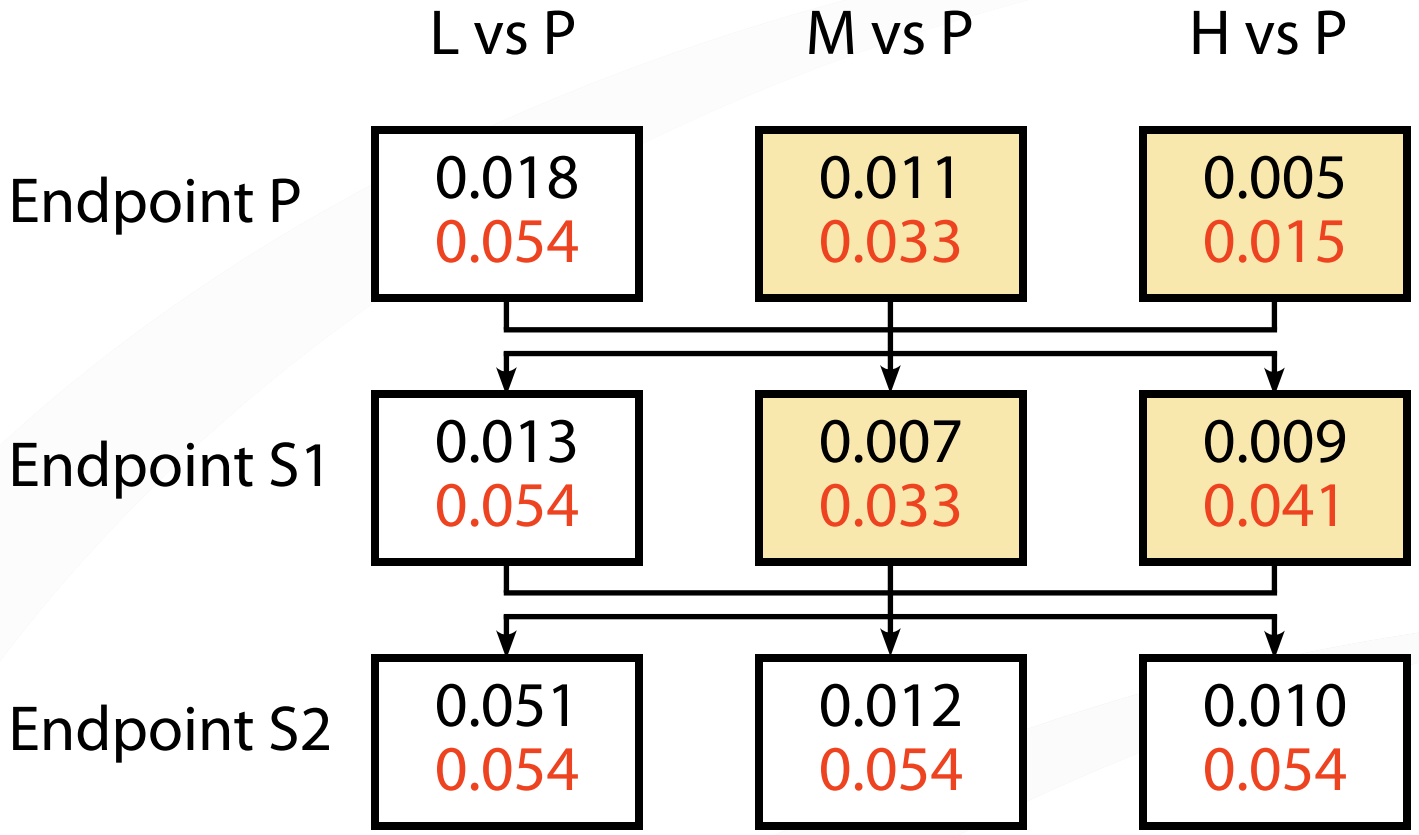
Logical restrictions



Diabetes trial

Parallel gatekeeping strategy

No logical restrictions



Extensions

Basic branching framework

Based on Bonferroni test

Account for correlation

Correlation among multiple endpoints

Correlation among multiple dose-control comparisons

Account for correlation via resampling (Westfall and Young, 1993)

Summary

Branching procedures

Efficient way to account for hierarchically ordered multiple objectives in clinical trials

Extend serial and parallel gatekeeping methods

Simple software implementation (SAS macro)

Closed testing principle

Control the familywise error rate in the strong sense

References

Chen, Luo, Capizzi. The application of enhanced parallel gatekeeping strategies. Statistics in Medicine. 2005; 24:1385-1397.

Dmitrienko, Offen, Westfall. Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. Statistics in Medicine. 2003; 22:2387-2400.

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Marcus, Peritz, Gabriel. On closed testing procedures with special reference to ordered analysis of variance. Biometrika. 1976; 63:655-660.

References

Westfall, Krishen. Optimally weighted, fixed sequence and gatekeeper multiple testing procedures. Journal of Statistical Planning and Inference. 2001; 99:25-41.

Westfall, Young. Resampling-Based Multiple Testing: Examples and Methods for P-Value Adjustment. New York: Wiley, 1993.