Multiple Comparisons for Multiple Endpoints and Multiple Doses

Ajit C. Tamhane
Northwestern University

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Institute of Mathematical Sciences
National University of Singapore
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Outline I

Outline II

Key References

- Book: *Multiple Testing Problems in Pharmaceutical Statistics*, co-edited by A. Dmitrienko, A. C. Tamhane and F. Bretz, Taylor & Francis (2009)
- Website: http://multxpert.com

1. Introduction

- 1.1 Classical Single Hypothesis Testing
- 1.2 Sources of Multiplicity in Clinical Trials
- 1.3 Regulatory Guidelines

1.1 Classical Single Hypothesis Testing

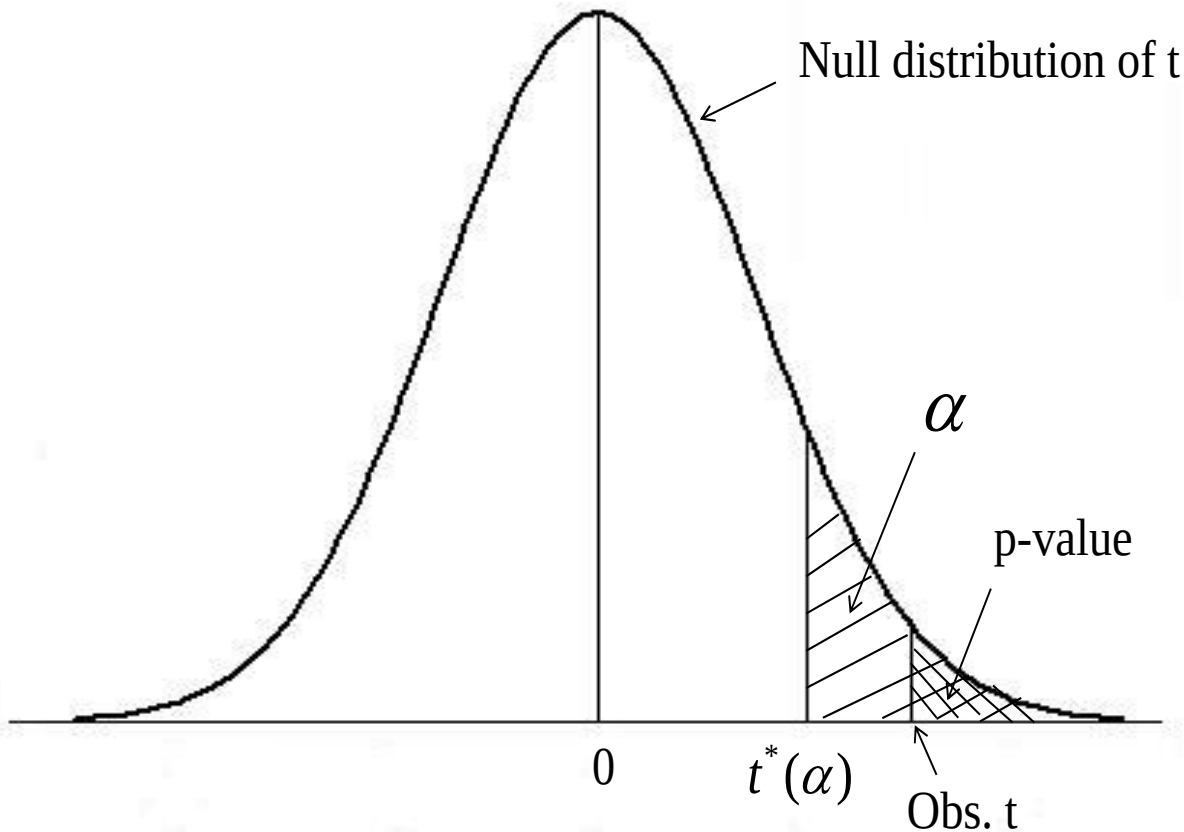
- A single a priori specified null hypothesis $H_0 : \delta = 0$ against an alternative hypothesis $H_1 : \delta > 0$, where $\delta =$ treatment effect.
- Type I error = Reject H_0 when H_0 is true = False positive, Type II error = Accept H_0 when H_1 is true = False negative
- $P(\text{Type I error}) \leq \alpha =$ Significance Level.
- Power $= 1-$ $P(\text{Type II error})$. Maximize power subject to α-requirement.
- Based on the data compute a test statistic

$$t = \frac{\widehat{\delta}}{\text{std. dev.}(\widehat{\delta})}$$

and its p-value.

- Reject H_0 if $t > t^*(\alpha)$ or equivalently if p-value $< \alpha$.

α-Level Test and p-Value



1.2 Sources of Multiplicity in Clinical Trials

- Multiple endpoints (efficacy and safety)
- Multiple treatment arms or doses of a drug
- Interim analyses (group sequential trials)
- Subgroup analyses
- Data-snooping or data-fishing
- Chance of false positives increases if no adjustment for multiplicity is made.
- Multiple test procedures (MTPs) control frequency of false positives.

1.3 Regulatory Guidelines

- FDA Multiplicity Guidance Document (due early 2012).
- ICH E9: "in confirmatory analyses, any aspects of multiplicity . . . should be identified in the protocol; adjustment should always be considered and the details of any adjustment procedure . . . should be set out in the analysis plan."

2. Error Rates

- 2.1 Familywise Error Rate (FWER)
- 2.2 False Discovery Rate (FDR)

2.1 Familywise Error Rate (FWER)

- A family is a collection of a priori stated null hypotheses

$$F = \{H_1, \ldots, H_n\}.$$

- Test statistics $t_1, t_2, \ldots, t_n$.
- p-values: $p_1, p_2, \ldots, p_n$.
- MTPs are commonly designed to control the Type I Familywise Error Rate (FWER):

$$\text{FWER} = P\{\text{Reject at least one true } H_i\} \leq \alpha$$

for any combination of true and false H_i: Strong control (Hochberg and Tamhane 1987).

2.2 False Discovery Rate (FDR)

- Benjamini & Hochberg (1995)
- Let $R = \sharp$ of rejections, $V = \sharp$ of false rejections. Then

$$\text{FDR} = E\left(\frac{V}{R}\right).$$

- Used in exploratory studies involving a very large number of hypotheses, e.g., microarrays.
- FDR not applicable in confirmatory trials with a few endpoints. We will use FWER throughout.

3. Examples

All clinical trial examples are from Eli Lilly (courtesy Dr. Alex Dmitrienko), but with modified data

- 3.1 Cardiovascular Trial
- 3.2 Alzheimer's Trial
- 3.3 Extensions and Other Problems

3.1 Cardiovascular Trial

- Trial to evaluate the effects of lisinopril on mortality and morbidity of patients with heart disease (similar to Packer et al. studies (1996. 1999) on amlodipine and lisinopril).
- Two co-primary endpoints:
  - All-cause mortality
  - All-cause mortality or all-cause hospitalization
- Win criterion: Win on *at least one* endpoint (classical multiple comparisons problem)

3.2 Alzheimer's Trial

- Trial to evaluate the effects of donepezil on cognition and global changes in patients with mild to moderate Alzheimer's disease.
- Two co-primary endpoints:
  - Alzheimer's disease assessment scale-Cognitive subscale (ADAS-Cog)
  - Clinician global impression change (CGIC)
- Win criterion: Win on *both* endpoints

3.3 Extensions and Other Problems

- Primary and secondary endpoints with logical restrictions
- Multiple doses of a drug tested on multiple endpoints
- Non-inferiority/superiority tests
- Gatekeeping procedures
- Overall efficacy (global tests, O'Brien 1985)

4. Methods for Constructing MTPs

- 4.1 Union-Intersection (At Least One) Method
- 4.2 Intersection-Union (All or None) Method
- 4.3 Closure Method

4.1 Union-Intersection (At Least One) Method

- c: critical constant to control FWER at α level.

$$\text{Reject at least one } H_i$$
$$\Longleftrightarrow$$
$$\text{At least one } t_i > c$$
$$\Longleftrightarrow$$
$$t_{\max} > c$$

- FWER is controlled if c is the upper α critical point of $t_{\max}$ under H_0: MAX test (Roy 1953):
- Bonferroni procedure: Rejects H_i if $t_i > c = t^*\left(\frac{\alpha}{n}\right)$ or $p_i < \frac{\alpha}{n}$.

4.2 Intersection-Union (All or None) Method

- c: critical constant to control FWER at α level.

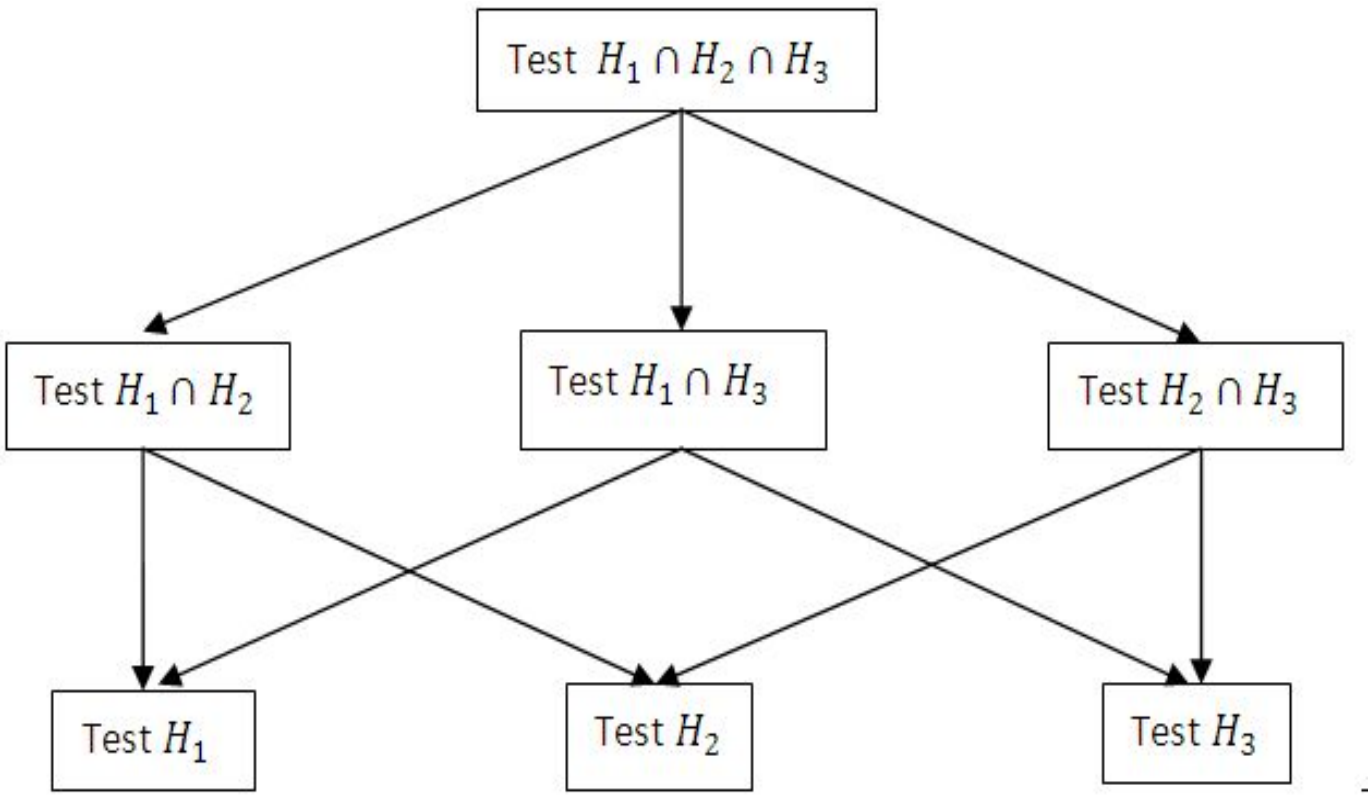
$$\text{Reject all } H_i$$
$$\Longleftrightarrow$$
$$\text{All } t_i > c$$
$$\Longleftrightarrow$$
$$t_{\min} > c$$

- FWER is controlled if c is the upper α critical point of a single t_i, i.e. $c = t^*(\alpha)$.
- Reject all H_i if $t_{\min} > t^*(\alpha)$ or $p_{\max} < \alpha$: MIN test (Berger 1982,Laska and Meisner 1989)
- No α-adjustment.

4.3 Closure Method

- Useful for constructing more powerful stepwise MTPs (Marcus, Peritz & Gabriel 1976).
- Test each intersection hypothesis using any α-level test starting with the full intersection of all elementary hypotheses.
- If any intersection hypothesis is accepted, accept all intersection hypotheses implied by it (ensures coherence).
- Strongly controls FWER $\leq \alpha$.
- In many cases shortcut stepwise procedures exist: Easy to use and transparent.

Closure Method: Example



5. Common p-Value Based MTPs

- 5.1 Holm Procedure
- 5.2 Simes Test
- 5.3 Hochberg Procedure

Reasons for Using p-Value Procedures

- Correlations between endpoints are unknown, so parametric procedures based on multivariate test statistics can't be exactly used.
- Marginal p-values are readily available (but ignore correlations).
- Marginal p-values may come from diverse tests, e.g., t-tests, χ^2-tests, logrank tests, etc.

5.1 Holm Procedure

- Holm (1979): Stepwise shortcut to a closed procedure that uses the Bonferroni test for each intersection hypothesis.
- Step-down algorithm

$$\begin{array}{ccccccc} H_{(1)} & & H_{(2)} & & & & H_{(n)} \\ p_{(1)} & \leq & p_{(2)} & \leq & \cdots & \leq & p_{(n)} \\ \frac{\alpha}{n} & & \frac{\alpha}{n-1} & & & & \frac{\alpha}{1} \end{array}$$

- Begin testing with $p_{(1)}$ & continue as long as you get rejections. If at the ith step $p_{(i)} > \frac{\alpha}{n-i+1}$ then accept $H_{(i)}$ and all the remaining hypotheses.
- Adjusted p-values:
  $\widetilde{p}_{(i)} = \max(\widetilde{p}_{(i-1)}, (n-i+1)p_{(i)}),\ i = 1, \ldots, n.$

5.2 Simes Test

- Simes (1986) Identity: If the p-values are independent then

$$P_{H_0}\left(p_{(1)} > \frac{\alpha}{n}, p_{(2)} > \frac{2\alpha}{n}, \ldots, p_{(n)} > \frac{\alpha}{1},\right) = 1 - \alpha.$$

- Reject H_0 at level α if at least one $p_{(i)} \leq \frac{i\alpha}{n}$.
- More powerful than the Bonferroni test, but requires the independence assumption (or positively correlated p-values, Sarkar and Chang 1997).
- Does not control FWER if used as an MTP, i.e., if we reject $H_{(i)}$ when $p_{(i)} \leq \frac{i\alpha}{n}$.

5.3 Hochberg Procedure

- Hochberg (1988): Conservative stepwise shortcut to a closed procedure that uses the Simes test for each intersection hypothesis. Exact shortcut: Hommel (1988).
- Step-up algorithm

$$\begin{array}{ccccccc} H_{(1)} & & H_{(2)} & & & & H_{(n)} \\ p_{(1)} & \leq & p_{(2)} & \leq & \cdots & \leq & p_{(n)} \\ \frac{\alpha}{n} & & \frac{\alpha}{n-1} & & & & \frac{\alpha}{1} \end{array}$$

- Begin testing with $p_{(n)}$ & continue as long as you get acceptances. If at the ith step $p_{(i)} < \frac{\alpha}{n-i+1}$ then reject $H_{(i)}$ and all the remaining hypotheses.
- Adjusted p-values:
  $\widetilde{p}_{(i)} = \min(\widetilde{p}_{(i+1)}, (n-i+1)p_{(i)}),\ i = 1, \ldots, n.$

6. MTPs for a priori Ordered Hypotheses

- 6.1 Fixed Sequence Procedure
- 6.2 Fallback Procedure

6.1 Fixed Sequence Procedure

- In some problems hypotheses are a priori ordered based on importance, e.g., ordered doses.

$$H_1 \to H_2 \to \cdots \to H_n.$$

- Fixed sequence procedure: Starting with H_1, reject each H_i if $p_i \leq \alpha$. Continue testing as long as rejections occur. Stop testing and accept all the remaining hypotheses if an acceptance occurs.
- No α-adjustment (Maurer, Hothorn & Lehmacher 1995).

6.2 Fallback Procedure

- Proposed by Wiens (2003).
- Assign weights $w_i > 0$ to hypotheses H_i $(i = 1, \ldots, n)$; $\sum_{i=1}^{n} w_i = 1$.
- At any step i test H_i at level α_i where

$$\alpha_i = \begin{cases} w_i \alpha & \text{if } H_{i-1} \text{ is accepted} \\ w_i \alpha + \alpha_{i-1} & \text{if } H_{i-1} \text{ is rejected} \end{cases}$$

- Fixed sequence procedure: Special case of fallback for $w_1 = 1, w_2 = \cdots = w_n = 0$.
- "Use it or lose it" principle.

Summary of Procedures

- In terms of power, Hochberg $>$ Holm $>$ Bonferroni.
- Hochberg requires p-values to be independent or positively correlated; no such restriction on Holm and Bonferroni.
- Fixed sequence and fallback used for a priori ordered hypotheses.
- Fallback is more flexible than fixed sequence.
- Whether fallback or fixed sequence is more powerful depends on the true effect sizes for ordered hypotheses and weights used by fallback.

7. Back to Examples

- 7.1 Cardiovascular Trial
- 7.2 Alzheimer's Disease Trial

7.1 Cardiovascular Trial

Placebo: $n = 1596$, Treatment: $n = 1568$, $\alpha = 0.025$

Endpoint	Event Rate (%)		z-statistic	1-sided p-value
	Placebo	Treatment		
E1	44.8	41.1	2.102	0.018
E2	83.8	80.8	2.211	0.014

7.1 Cardiovascular Trial

- Bonferroni Procedure: Both $p_1 = 0.018$ and $p_2 = 0.014 > \alpha/2 = 0.0125$, so declare both not significant.
- Holm Procedure: $p_{(1)} = p_2 = 0.014 > 0.0125$, so stop testing and declare both not significant.
- Hochberg Procedure: $p_{(2)} = p_1 = 0.018 < \alpha = 0.025$, so stop testing and declare both significant.
- Fixed Sequence Procedure: $p_1 = 0.018 < \alpha = 0.025$ and $p_2 = 0.014 < \alpha = 0.025$, so declare both significant.
- Fallback Procedure: Suppose $w_1 = 0.8, w_2 = 0.2$. $p_1 = 0.018 < 0.8\alpha = 0.020$ and $p_2 = 0.014 < 0.2\alpha + 0.8\alpha = 0.025$, so declare both significant.

7.1 Cardiovascular Trial

Adjusted p-Values

(Raw p-Values: $p_1 = 0.018, p_2 = 0.014$)

Procedure	Endpoint	
	E1	E2
Bonferroni	0.036	0.028
Holm	0.028	0.028
Hochberg	0.018	0.018
Fixed Sequence	0.018	0.018
Fallback	0.023	0.014

7.2 Alzheimer's Disease Trial

Placebo: $n = 161$, Treatment: $n = 167$, $\alpha = 0.025$

Endpoint	Mean and Std. Error		t-statistic	1-sided p-value
	Placebo	Treatment		
E1	2.1 (0.583)	0.4 (0.573)	2.080	0.0192
E2	4.4 (0.087)	4.1 (0.085)	2.469	0.0135

$p_{\max} = 0.0192 < 0.025$. So the treatment is effective.

8. Dose Comparisons with a Placebo

- 8.1 Dunnett Procedure
- 8.2 Major Depressive Disorder Trial Example

8.1 Dunnett Procedure

- Compare $m \geq 2$ increasing doses with a zero dose (control).
- Assume that data from Dose i is distributed $N(\mu_i, \sigma^2)$.
- Hypotheses $H_i : \mu_i - \mu_0 = 0$ vs. $\overline{H}_i : \mu_i - \mu_0 > 0$.
- Assume common sample size n per dose.
- Test statistics:

$$t_i = \frac{\overline{y}_i - \overline{y}_0}{\widehat{\sigma}\sqrt{2/n}} \ (i = 1, \ldots, m).$$

- p-values: $p_i \ (i = 1, \ldots, m)$.

8.1 Dunnett Procedure

- Dunnett Procedure: A parametric alternative to the Bonferroni procedure. Exploits known correlations (depend on the sample sizes) between the test statistics.
- Based on the union-intersection method: Reject H_i if $t_i > c$ where $c =$ upper α critical point of $t_{\max}$.
- To evaluate c, need the joint distribution of $t_1, \ldots, t_n$: Multivariate t-distribution.
- Table of Multivariate t and Bonferroni c-values ($\alpha = 0.05$, degrees of freedom $= \infty$)

m	1	2	3	4	5
Mult. c	1.645	1.916	2.062	2.160	2.234
Bonf. c	1.645	1.960	2.127	2.241	2.326

8.2 Major Depressive Disorder Trial

- Placebo-controlled parallel arm trial
- Four dose levels (D1: 10 mg/day, D2: 20 mg/day, D3: 40 mg/day, D4: 60 mg/day) + D0: Placebo
- 432 patients randomized to 5 dose groups
- Endpoint: Mean reduction from baseline in 17-item Hamilton Depression Scale (HAMD-17)
- Data

Dose	D0	D1	D2	D3	D4
n	85	87	88	87	85
$\overline{y}$	6.12	6.85	7.08	7.50	7.22

$$\widehat{\sigma} = 6.6$$

8.2 Major Depressive Disorder Trial

t-Statistics and p-Values, $\alpha = .05$

	D1 vs. D0	D2 vs. D0	D3 vs. D0	D4 vs. D0
t_i	1.464	1.925	2.767	2.206
p_i	0.072	0.027	0.003	0.017

- Dunnett procedure: Compares t-statistics with $c = 2.160$ (for $m = 4$). Declares doses D3 and D4 significantly better than D0.
- Step-down Dunnett procedure: $t_3 > 2.160, t_4 > 2.062, t_2 > 1.916, t_1 < 1.645$. Stops testing and declares doses D2, D3 and D4 significantly better than D0.

8.2 Major Depressive Disorder Trial

t-Statistics and p-Values, $\alpha = .05$

	D1 vs. D0	D2 vs. D0	D3 vs. D0	D4 vs. D0
t_i	1.464	1.925	2.767	2.206
p_i	0.072	0.027	0.003	0.017

- Bonferroni procedure: Compares t-statistics with $c = 2.241$ (for $m = 4$) or p-values with $.05/4 = .0125$. Declares dose D3 significantly better than D0.
- Holm procedure: $p_3 < .0125, p_4 < .0167, p_2 > .025$. Stops testing and declares doses D3 and D4 significantly better than D0 (same result with Hochberg procedure).

9. Gatekeeping Procedures

- 9.1 Why Gatekeeping?
- 9.2 Assumptions and Notation
- 9.3 Types of Gatekeeping
- 9.4 Serial Gatekeeping
- 9.5 Parallel Gatekeeping
- 9.6 General Gatekeeping

9.1 Why Gatekeeping?

- Clinical trials often involve multiple hierarchically ordered hypotheses with logical restrictions, e.g., multiple endpoints, multiple patient subgroups, noninferiority-superiority tests.
- Sponsors like to enrich product labels by additional claims.
- O'Neill (1997): "Secondary endpoints cannot be validly analyzed if the primary endpoint does not demonstrate clear statistical significance."
- CPMP Points to Consider Document (2002): "Additional claims... [for] secondary variables... are possible only after the primary objective of the clinical trial has been achieved, and if the respective questions were pre-specified, and were part of an appropriately planned statistical analysis strategy."
- FDA Multiplicity Guidance Document (due early 2012) is expected to have a similar requirement.

9.2 Assumptions and Notation

- $n \geq 2$ hypotheses, $H_1, \ldots, H_n$, grouped into $m \geq 2$ ordered families $F_1, \ldots, F_m$.
- Family $F_j = \{H_i : i \in N_j\}$ where $N_1 = \{1, \ldots, n_1\}, N_j = \{n_1 + \ldots + n_{j-1} + 1, \ldots, n_1 + \ldots + n_j\}$.
- Family F_j consists of n_j hypotheses with $\sum_{j=1}^{m} n_j = n$.
- F_j is a gatekeeper for F_{j+1}, $j = 1, 2, \ldots, m-1$.
- Strong control of FWER:

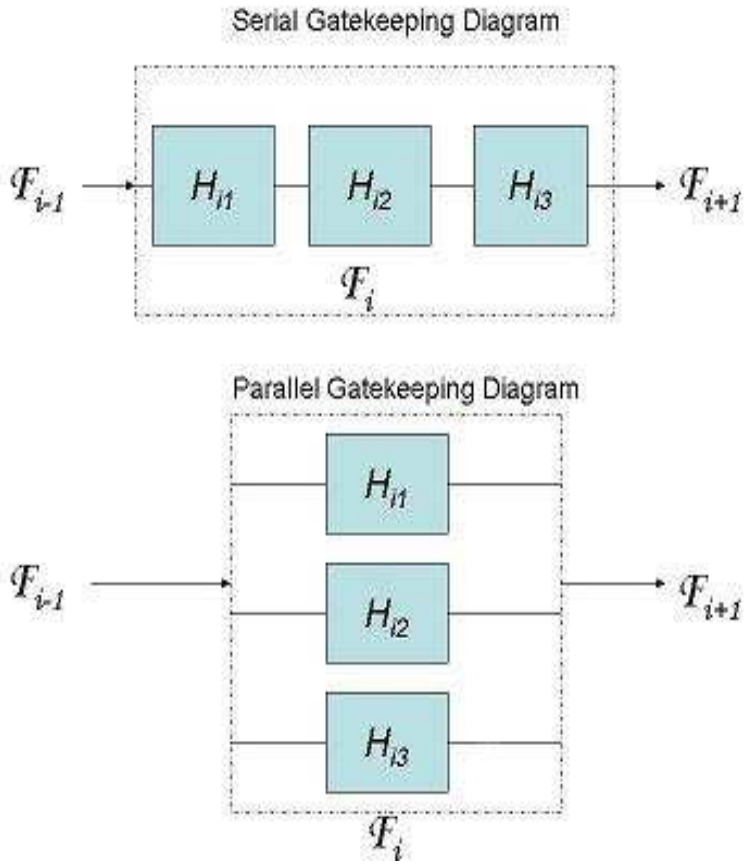
$$\text{FWER} = P\{\text{Reject at least one true } H_i\} \leq \alpha.$$

- Independence Condition: Inferences on $H_i \in F_j$ don't depend on inferences on $H_i \in F_k$ for $k > j$ (desirable but not essential).

9.3 Types of Gatekeeping

- If the gatekeeper F_j is passed then hypotheses in F_{j+1} are *testable* (i.e., they must be tested to make accept/reject decision); otherwise all hypotheses in F_k for $k > j$ are *non-testable* (i.e., are automatically accepted).
- Serial gatekeeping: Gatekeeper F_j is passed iff all $H_i \in F_j$ are rejected (Maurer, Hothorn & Lehmacher 1995).
- Parallel gatekeeping: Gatekeeper F_j is passed iff at least one $H_i \in F_j$ is rejected (Dmitrienko, Offen & Westfall 2003).
- General gatekeeping (Dmitrienko, Wiens, Tamhane & Wang 2007, Dmitrienko and Tamhane 2011a,b, Dmitrienko, Kordzkhia and Tamhane 2011).

Serial and Parallel Gatekeeping



Serial and Parallel Gatekeeping: Examples

- Serial gatekeeping example: Alzheimer disease trial
  - Primary endpoints: (i) Alzheimer disease assessment scale - Cognitive subscale (ADAS-COG), (ii) Clinical global impression change (CGIC). Both must be significant.
  - Secondary endpoints: Biochemical and imaging markers
- Parallel gatekeeping example: Osteoporosis trial in post-menopausal women
  - Primary endpoints: (i) Incidence of new vertebral fractures, (ii) Incidence of new invasive breast cancer
  - Secondary endpoint: Incidence of new non-vertebral fractures

9.4 Serial Gatekeeping

- Maurer, Hothorn & Lehmacher (1995).
- Test each F_j at local level α using any procedure. Proceed to test F_{j+1} iff all $H_i \in F_j$ are rejected.
- Use the Intersection-Union (IU) procedure which tests each $H_i \in F_j$ at level α.
- Generalization of the fixed sequence test.
- This procedure can be derived using the closure method, hence controls FWER strongly.

9.5 Parallel Gatekeeping

- Dmitrienko, Westfall & Offen (2003), Dmitrienko, Tamhane, Wang & Chen (2006), Guilbaud (2007), Dmitrienko, Tamhane & Wiens (2008).
- Stepwise procedure based on the "use it or lose it" principle (underlies the fixed sequence and fallback tests).
  - If a hypothesis is rejected then the α allocated to it is not spent and can be reused to test other hypotheses.
  - If a hypothesis is accepted then the α allocated to it is spent and cannot be reused to test other hypotheses.
- The error rate function quantifies the "unused" α that can be carried forward from one family to the next.

Error Rate Function: Definition

- Consider a single family $F = \{H_1, H_2, \ldots, H_n\}$ and let $N = \{1, 2, \ldots, n\}$.
- Let $H(I) = \bigcap_{i \in I} H_i$ for $I \subseteq N$ be an intersection hypothesis.
- For fixed α, the error rate function of a procedure is

$$e(I|\alpha) = \sup_{H(I)} P\left\{\text{Reject at least one } H_i,\ i \in I \middle|\ H(I)\right\}.$$

- For the Bonferroni procedure: $e(I|\alpha) = \frac{|I|}{n}\alpha$.
- $e(\emptyset|\alpha) = 0$, $e(I|\alpha) \leq e(J|\alpha)$ if $I \subseteq J$, $e(N|\alpha) = \alpha$.

Separable Procedures

- A procedure is separable if its error rate function satisfies

$$e(I|\alpha) < \alpha \text{ if } I \subset N \text{ and } e(N|\alpha) = \alpha.$$

- Single-step procedures, e.g., Bonferroni and Dunnett, are separable; stepwise procedures, e.g., Holm, Hochberg, Hommel and fallback, are non-separable.
- These stepwise procedures can be made separable by using a convex combination of the critical constants of stepwise and single-step procedures (e.g., Bonferroni or Dunnett).
- We call such hybrid stepwise procedures *truncated procedures*.
- In terms of power, non-separable procedures $>$ truncated procedures $>$ separable procedures.

Truncated Holm Procedure

- Compare ordered p-values, $p_{(j)}$, with the critical constants

$$\left[\frac{\gamma}{n-j+1}+\frac{1-\gamma}{n}\right]\alpha \text{ for } j=1,2,\ldots,n.$$

- $\gamma=0$ gives Bonferroni and $\gamma=1$ gives Holm.
- The error rate function:

$$e(I|\alpha)=\left[\gamma+(1-\gamma)\frac{|I|}{n}\right]\alpha$$

  if $|I|>0$ and $e(I|\alpha)=0$ if $|I|=0$.
- Truncated Holm is less powerful than Holm but more powerful than Bonferroni.

Parallel Gatekeeping: Stepwise Procedure

- Specify procedures $\mathcal{P}_1, \ldots, \mathcal{P}_m$ for families $F_1, \ldots, F_m$. The first $m-1$ procedures must be separable. $\mathcal{P}_m$ can be non-separable.
- Step 0: Set $\alpha_1 = \alpha$.
- Step j: For $j = 1, \ldots, m-1$, test F_j using $\mathcal{P}_j$ at level α_j. Let A_j be the index set of accepted hypotheses. Set

$$\alpha_{j+1} = \alpha_j - e_j(A_j|\alpha_j).$$

- Step m: Test F_m using $\mathcal{P}_m$ at level α_m.
- Note $\alpha_{j+1} = 0$ if $A_j = N_j$: parallel gatekeeping condition.
- Can test F_{j+1} when $A_j \subset N_j$ iff $\alpha_{j+1} > 0$ iff $\alpha_j > e_j(A_j|\alpha_j)$: separability condition.

Parallel Gatekeeping Stepwise Procedure: Example 1

- Suppose $\mathcal{P}_1, \ldots, \mathcal{P}_{m-1}$ are Bonferroni and $\mathcal{P}_m$ is any FWER controlling procedure.
- Let $a_j = |A_j| = \sharp$ accepted hypotheses, $r_j = |R_j| = \sharp$ rejected hypotheses. Then

$$\begin{aligned} \alpha_{j+1} &= \alpha_j - e_j(A_j|\alpha_j) \\ &= \alpha_j - \left(\frac{a_j}{n_j}\right)\alpha_j \\ &= \left(\frac{r_j}{n_j}\right)\alpha_j \\ &= \prod_{i=1}^{j}\left(\frac{r_i}{n_i}\right)\alpha. \end{aligned}$$

- More rejections $\Rightarrow$ More α carried forward, $r_j = 0 \Rightarrow$ procedure stops.

Parallel Gatekeeping Stepwise Procedure: Example 2

- $\alpha = .05$
- $\mathcal{P}_1$ for F_1 (Primary Endpoints): Bonferroni
- $\mathcal{P}_2$ for F_2 (Secondary Endpoints): Hochberg

F_i	Endpoint	p	α_i	Crit. Value	Result
F_1	P_1	.031	.05	.025	NS
	P_2	.013	.05	.025	S
F_2	S_1	.039	.025	.025	NS
	S_2	.027	.025	.0125	NS

$$\alpha_2 = \alpha_1 - (a_1/n_1)\alpha_1 = \alpha - (1/2)\alpha = .025.$$

Parallel Gatekeeping Stepwise Procedure: Example 2

$\mathcal{P}_1$ for F_1 (Primary Endpoints): Truncated Holm ($\gamma = 0.5$)
$\mathcal{P}_2$ for F_2 (Secondary Endpoints): Hochberg

F_i	Endpoint	p	α_i	Crit. Value	Result
F_1	P_1	.031	.05	.0375	S
	P_2	.013	.05	.025	S
F_2	S_1	.039	.05	.05	S
	S_2	.027	.05	.025	S

1. Truncated Holm constant for comparing $p = .031$:

$$\left[\frac{0.5}{1} + \frac{1 - 0.5}{2}\right](.05) = .0375.$$

2. $\alpha_2 = \alpha = .05$.

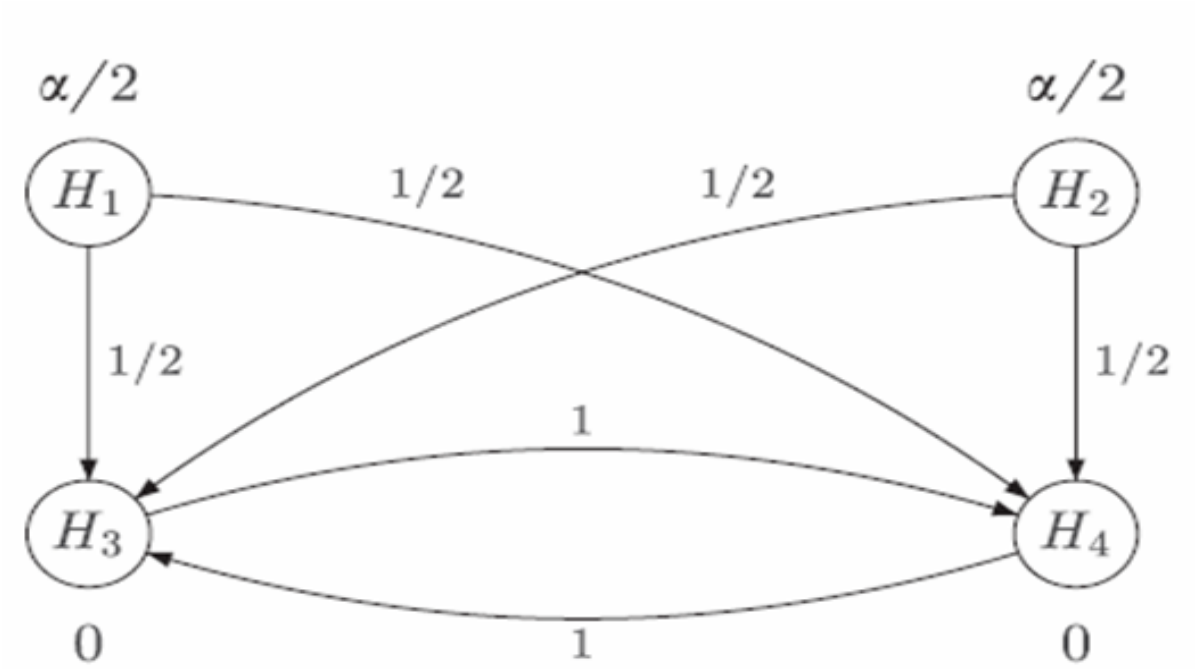
Choice of Truncation Parameter γ

- γ must be prespecified —not selected in light of the data.
- Higher the γ, higher the power of the procedure for the primary family.
- If higher power for the primary family does not result in rejection of more hypotheses then a smaller α carried to the next family $\Rightarrow$ less power for secondary family.
- If higher power for the primary family results in rejection of more hypotheses then a larger α could be carried to the next family $\Rightarrow$ higher power for secondary family.
- Generally, higher power in the primary family is at the expense of lower power for the secondary family.

Graphical Procedures

- Bretz, Maurer, Brannath and Posch (2009)
- $\mathcal{P}_1$: Bonferroni, $\mathcal{P}_2$: Holm

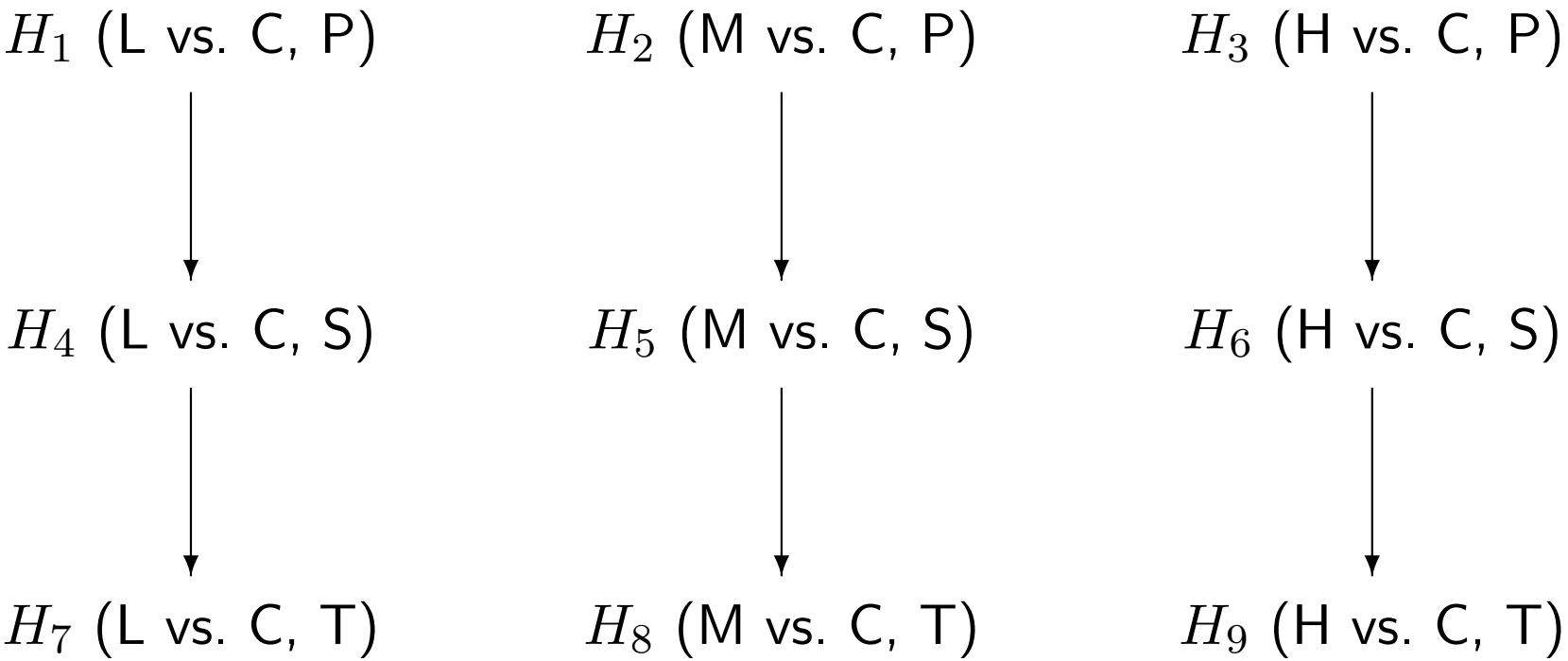
Parallel Gatekeeping Procedure for 2 Families



9.6 General Gatekeeping

- More complex clinical decision rules involving multiple objectives do not fit in the simple serial/parallel framework.
- Example 1: Diabetes Trial
  - Three Doses (High, Medium, Low) + Control with 3 Endpoints
  - Primary endpoint: Hemoglobin A1c
  - Secondary endpoint: Fasting serum glucose
  - Tertiary endpoint: HDL cholesterol.
  - For each dose, determine significant endpoints conditional on all higher-ranked endpoints being significant.

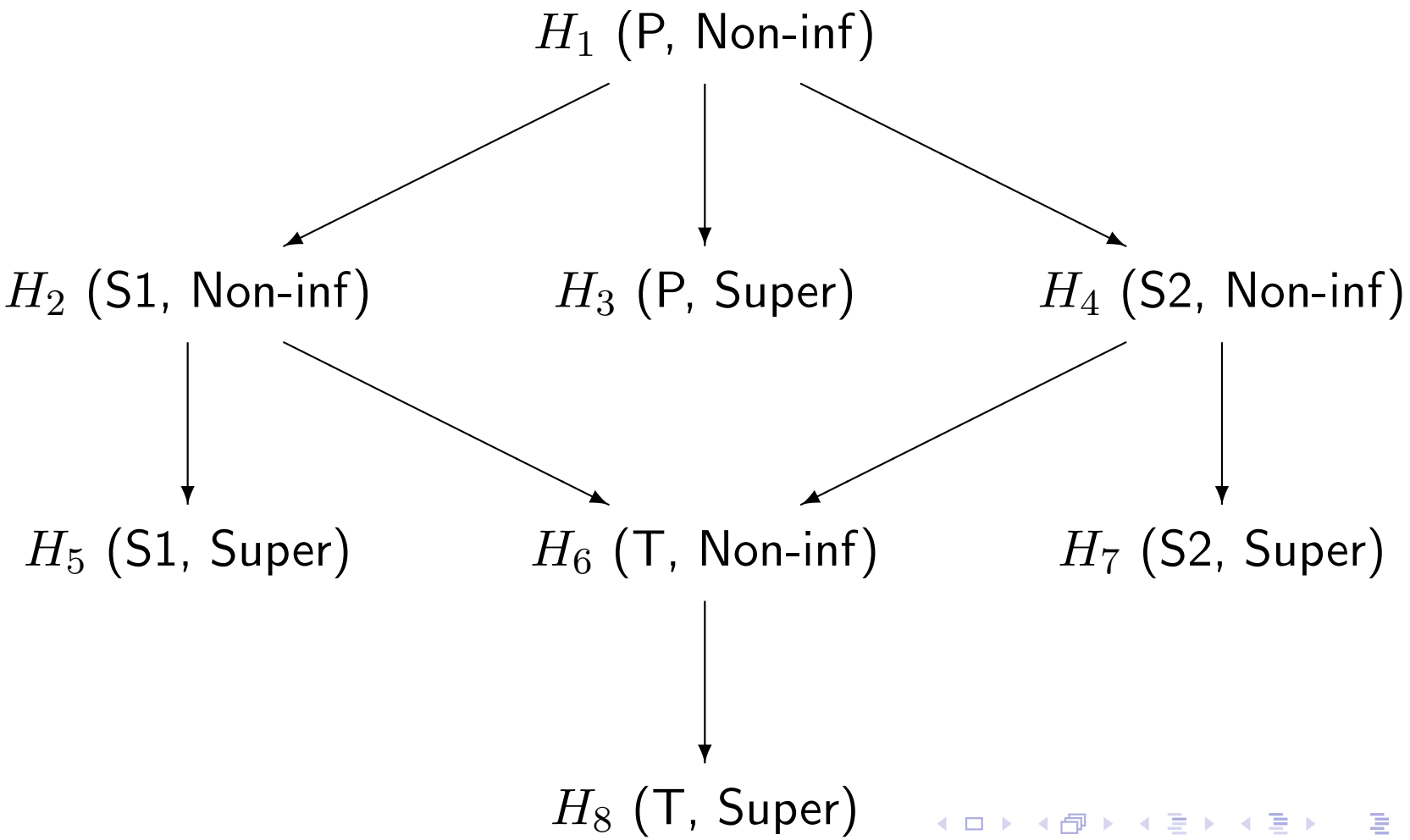
Diabetes Trial Example: Tree Diagram



Example 2: Hypertension Trial

- Primary endpoint (P): Mean reduction in systolic blood pressure.
- Two secondary endpoints (S1 and S2): Mean reduction in diastolic blood pressure and proportion of patients with controlled systolic/diastolic blood pressure.
- Tertiary endpoint (T): Average blood pressure based on ambulatory blood pressure monitoring.
- Test superiority conditional on showing noninferiority for each endpoint subject to their hierarchical ordering.

Hypertension Example: Tree Diagram



References on General Gatekeeping

- Tree-structured gatekeeping: Dmitrienko, Wiens, Tamhane & Wang (2007).
- Mixture gatekeeping: Dmitrienko & Tamhane, A.C. (2011a, 2011b), Dmitrienko, Kordzakhia & Tamhane (2011).
- Superchain procedures: Dmitrienko & Kordzakhia (2011)

10. Take-Home Lessons

- Multiplicity is omnipresent in clinical trials and causes Type I error inflation.
- Proper multiplicity adjustment is necessary to control Type I error inflation via control of FWER especially in confirmatory clinical trials.
- Single-step and more powerful stepwise multiple test procedures are easy to use to deal with standard multiple endpoints/multiple dose comparisons.
- Complex multiple test procedures, called gatekeeping procedures, are required when hypotheses are hierarchically ordered and logically related.

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