アダプティブデザインの理論の概要

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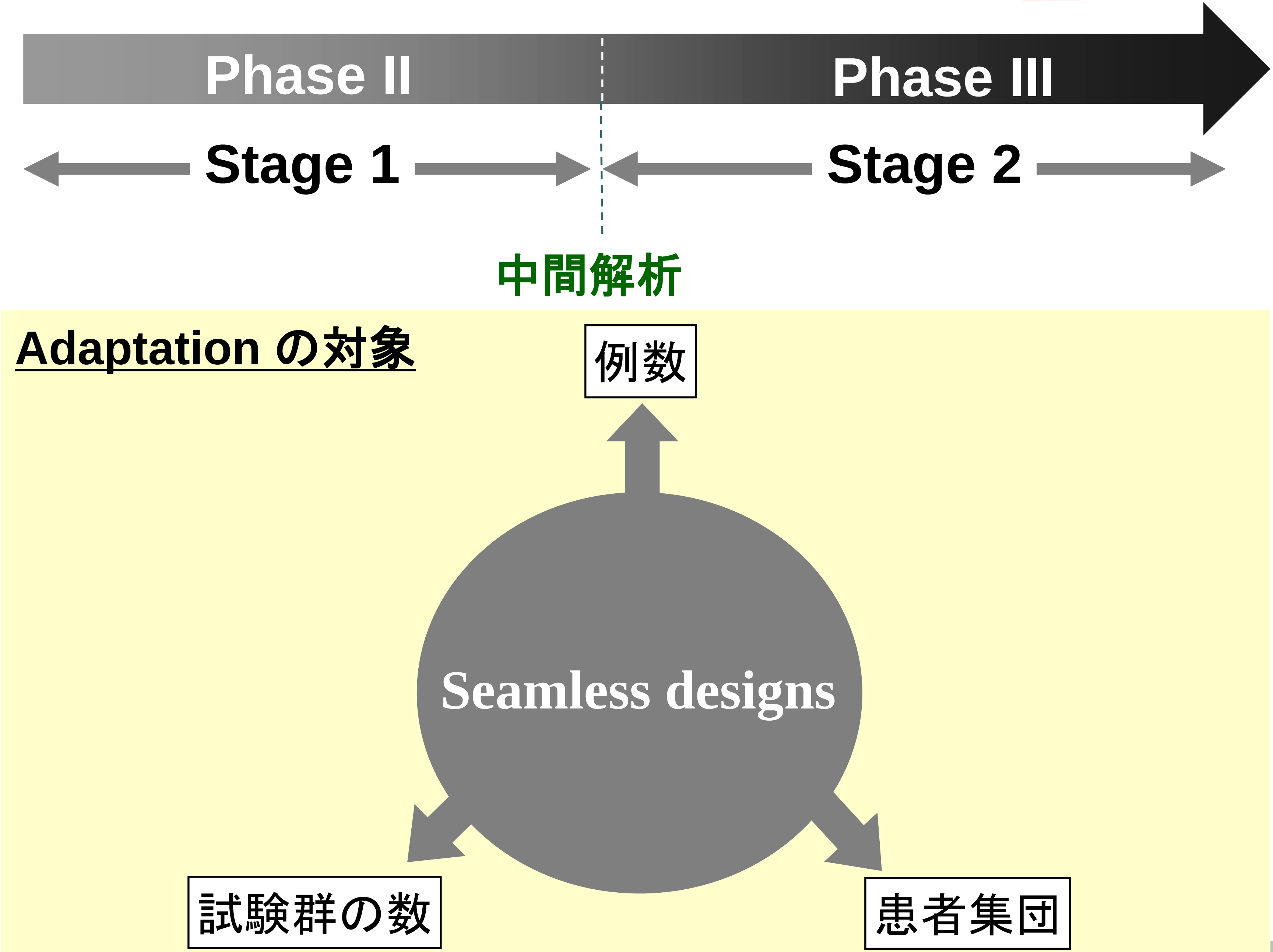
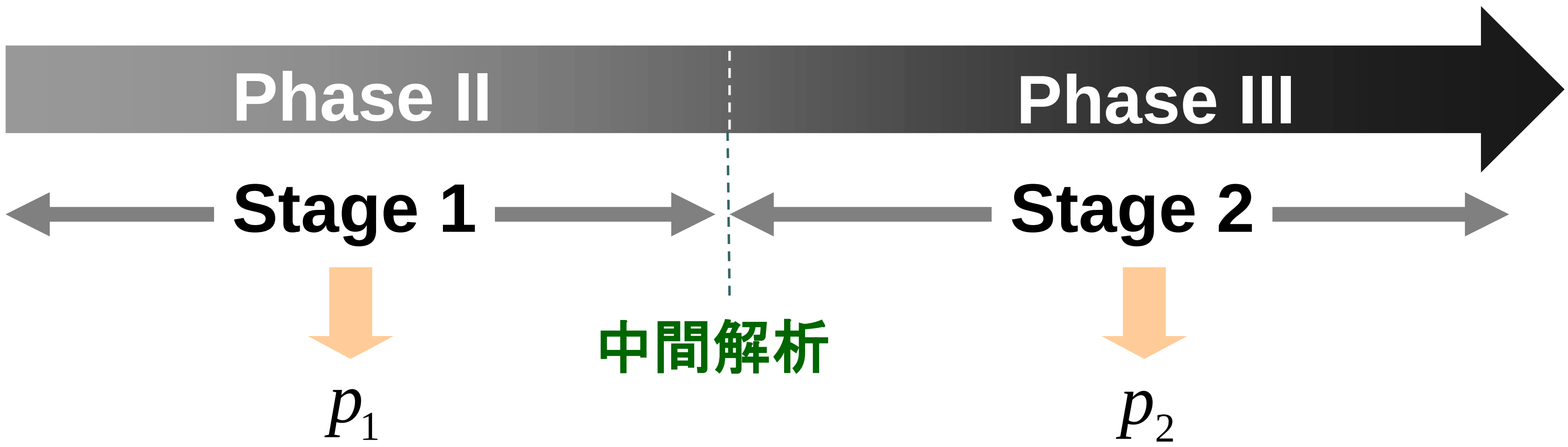
Adaptive seamless designs



Combination tests in adaptive seamless designs

2ステージの場合の Combination test



- p_k : Stage k から得られる片側p値

- Fisher's (product) combination test
- (Weighted) inverse normal combination test

Fisher's combination test

Stage 1 | Stage 2

p_1 | p_2

中間解析

- $p_k \sim U(0,1)$
- p_k ：独立

$$-\log p \sim \mathrm{Exp}(1) = \frac{1}{2}\chi_2^2$$

$$-\log(p_1 p_2) \sim \frac{1}{2}\chi_4^2$$

$$\therefore -\log(p_1 p_2) > \frac{1}{2}\chi_{4,1-\alpha}^2$$

$$C(p_1, p_2) = p_1 \cdot p_2 \le c = \exp(-\chi_{4,1-\alpha}^2 / 2)$$

Bauer (1989); Bauer & Köhne (1994)

Inverse normal combination test

Stage 1 | Stage 2

p_1 中間解析 p_2

$$C(p_1, p_2) = 1 - \Phi\left(w_1 \cdot \Phi^{-1}(1 - p_1) + w_2 \cdot \Phi^{-1}(1 - p_2)\right)$$

- $w_1^2 + w_2^2 = 1, \quad 0 < w_k < 1$

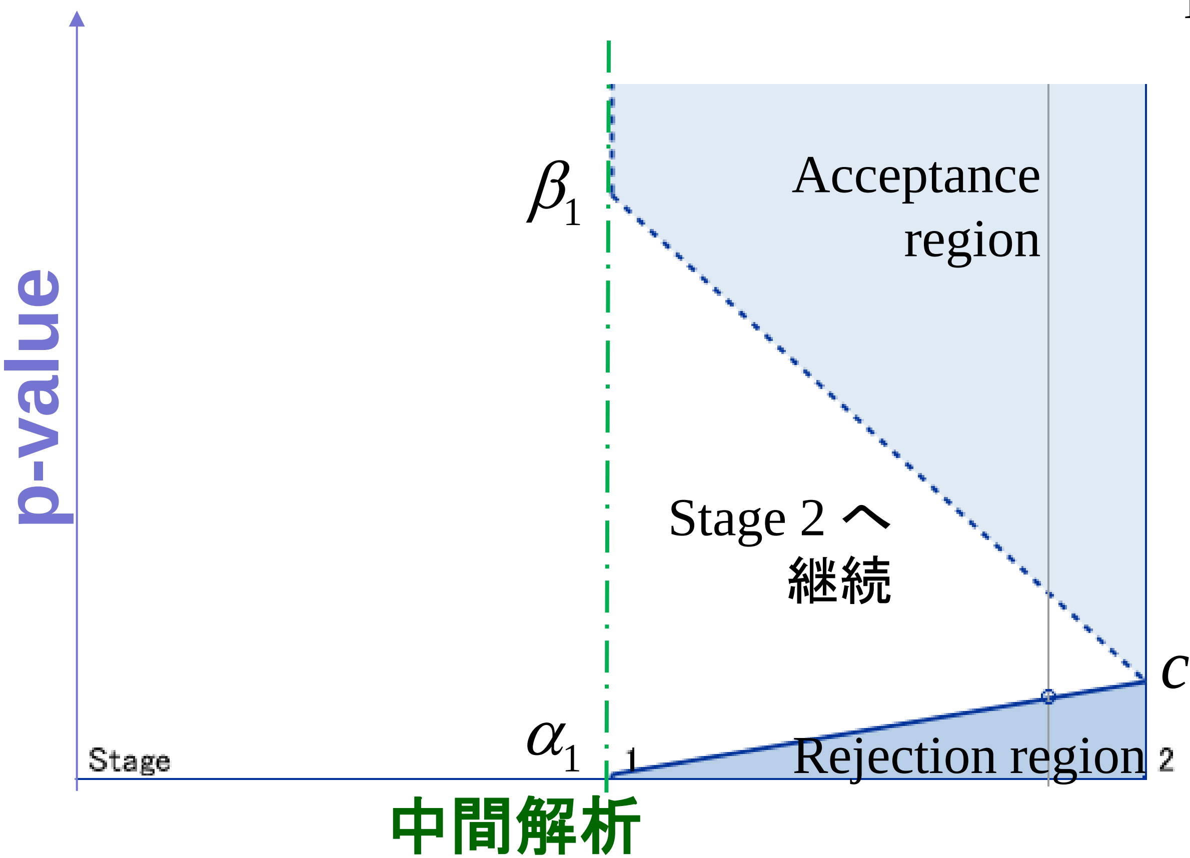
  $w_1 = \sqrt{n_1/(n_1 + n_2)}, \quad w_2 = \sqrt{n_2/(n_1 + n_2)}$
- w_k: Stage k に対する重み (事前規定)
- n_k: Stage k におけるサンプルサイズ (事前規定)
- $\Phi(\cdot)$ ：標準正規分布の累積分布関数

Lehmacher & Wassmer (1999); Cui, Hung, Wang (1999)

帰無仮説 H の下での Combination test の考え方

$$\alpha_1 + \int_{\alpha_1}^{\beta_1}\int_0^1 I\{C(x,y) \le c\}dydx = \alpha \qquad I\{\cdot\}\begin{cases} 1 & C(p_1, p_2) \le c \\ 0 & \text{otherwise} \end{cases}$$

Brannath, Posch, Bauer (2002)



- $p_k \sim U(0,1)$
- p_k : 独立

Conditional error function principle

- Conditional error function:
  - $A(p_1) = P(\text{reject} \quad H \mid p_1)$

- For combination tests

$$A(p_1) = \begin{cases} 1 & p_1 \le \alpha_1 & \text{: 有効中止} \\ \max\limits_{x \in [0,1]} \{x \mid C(p_1, x) \le c\} & \alpha_1 < p_1 \le \beta_1 & \text{: Stage 2 へ継続} \\ 0 & p_1 > \beta_1 & \text{: 無効中止} \end{cases}$$

Posch & Bauer (1999)

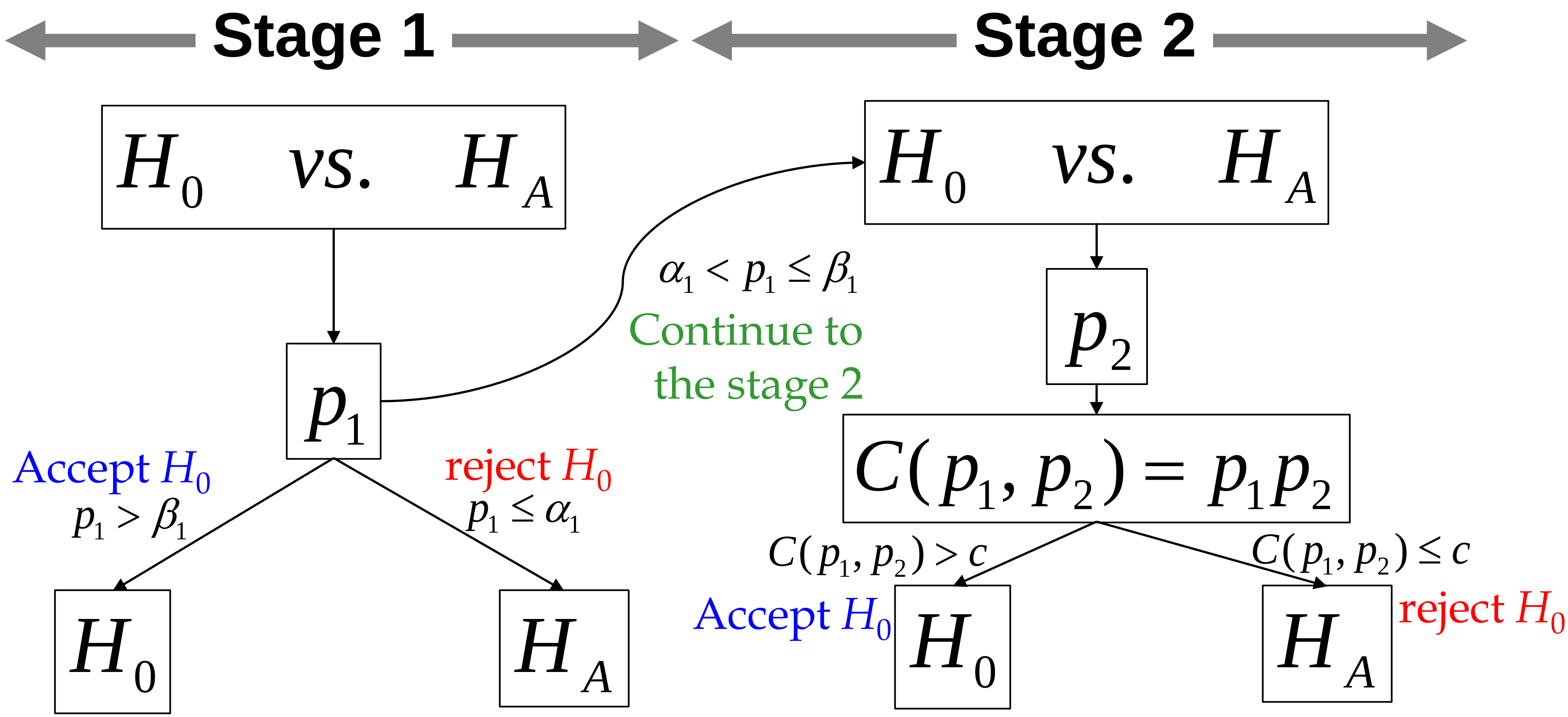
- 最終解析： $p_2 < A(p_1)$ ⇒ reject H

Stage 2 へ継続した場合

$$A(p_1) = \begin{cases} c / p_1 & \text{: Fisher's combination test} \\ 1 - \Phi\left(\dfrac{\Phi^{-1}(1-c) - w_1 \Phi^{-1}(1-p_1)}{w_2} \right) & \text{: Inverse normal combination test} \end{cases}$$

Multiple testing procedures in adaptive seamless designs

Fisher’s combination test による多重性の調整



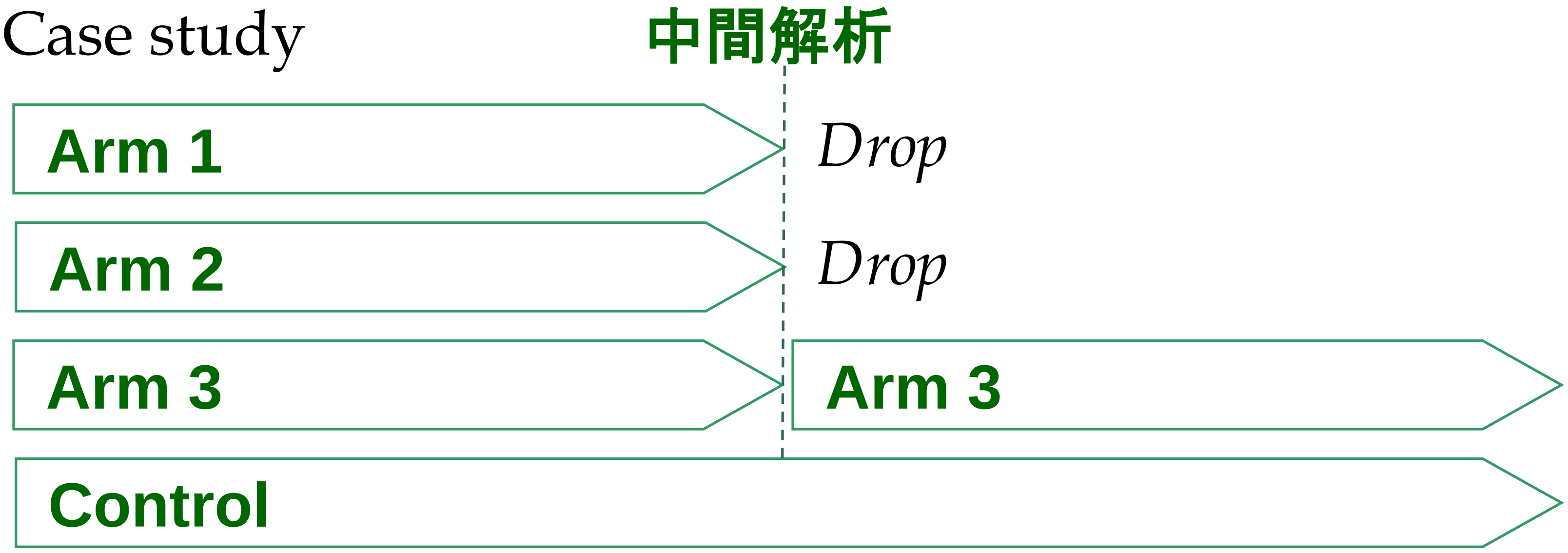
Bretz et al. (2006)

$$\{p_1 \le \alpha_1\} \cup [\{\alpha_1 < p_1 \le \beta_1\} \cap \{p_1 p_2 \le c\}] = \alpha$$

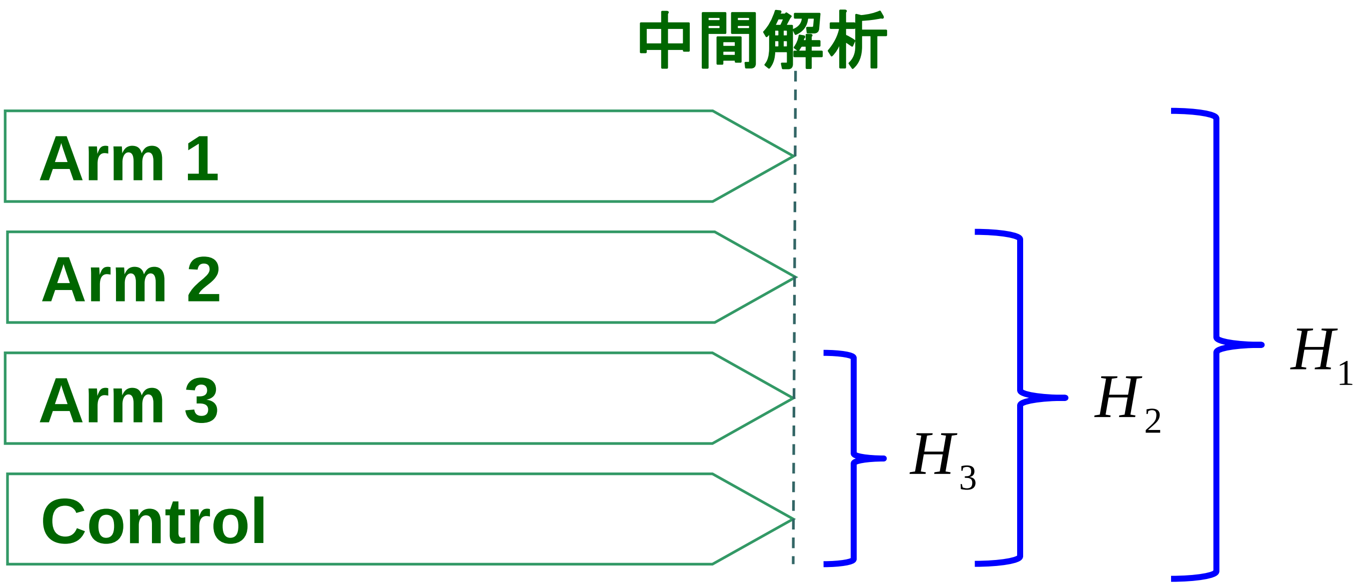
$$\alpha_1 + \int_{\alpha_1}^{\beta_1} \int_0^{c/p_1} dp_2 dp_1 = \alpha_1 + c(\log \beta_1 - \log \alpha_1) = \alpha$$

Adaptive treatment selection designs

- Case study

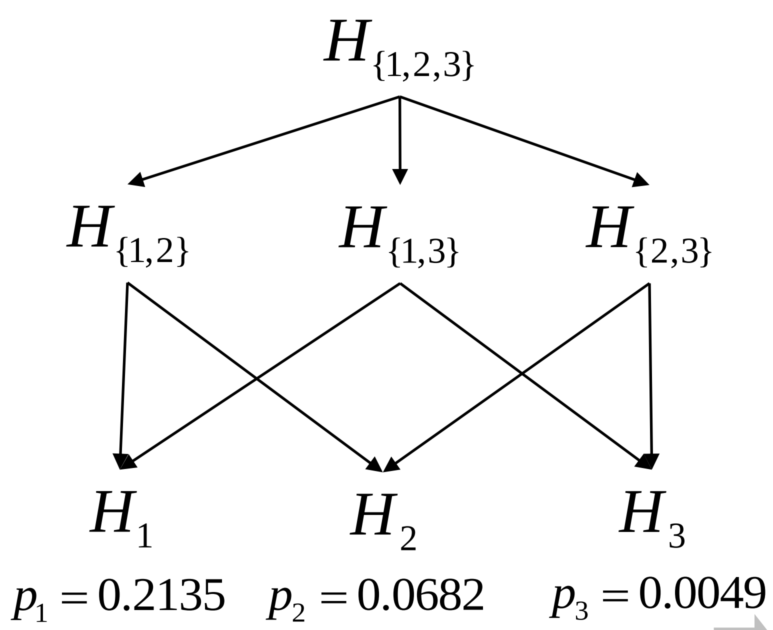


Case study: 中間解析における閉手順

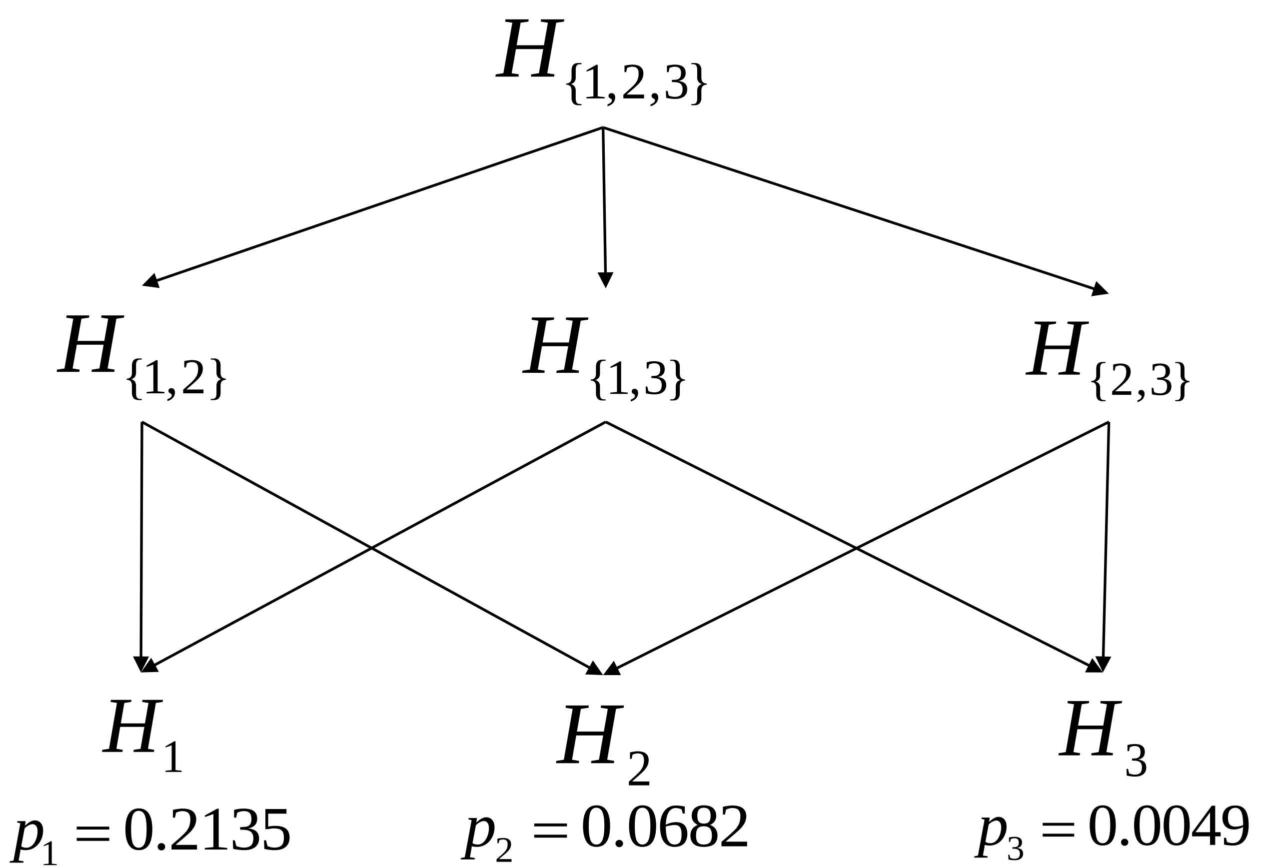


中間解析の結果

i	Observed mean value	Unadjusted p-value
0	0	-
1	0.8	0.2135
2	1.5	0.0682
3	2.6	0.0049



Step 1



Bonferroni test

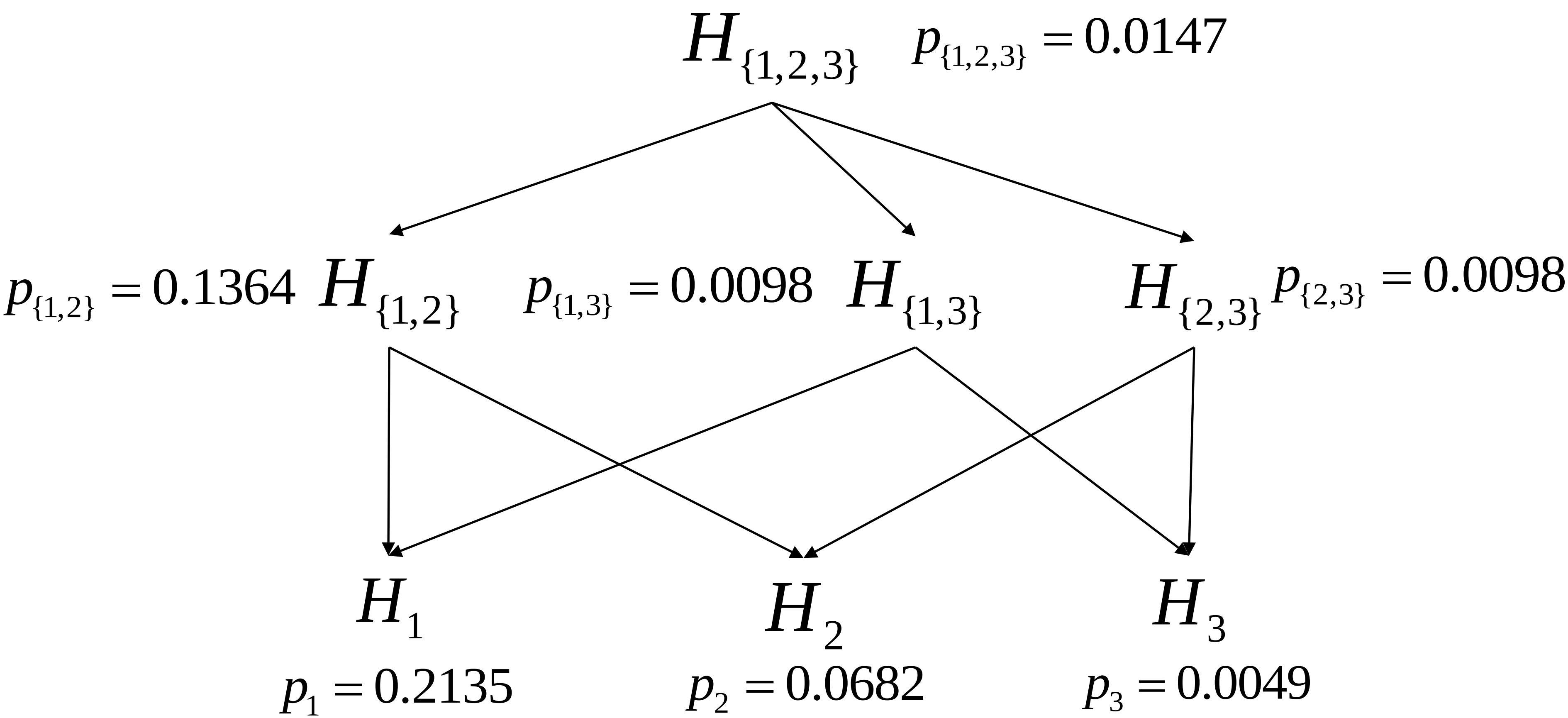
$$p_{(1)} = 0.0049, p_{(2)} = 0.0682, p_{(3)} = 0.2135$$

$$p_{\{1,2\}} = 0.1364, p_{\{1,3\}} = p_{\{2,3\}} = 0.0098, p_{\{1,2,3\}} = 0.0147$$

Step 2

Stopping boudaries

$\alpha_1 = 0.0054, \quad \beta_1 = 0.1, \quad c = 0.0359 \quad \text{for} \quad \alpha = 0.025$



Step 3

Stopping boudaries

$\alpha_1 = 0.0054, \quad \beta_1 = 0.1, \quad c = 0.0359$ for $\alpha = 0.025$

Continue to the stage 2

$H_{\{1,2,3\}}$ $\quad p_{\{1,2,3\}} = 0.0147$ $\quad \alpha_1 < p_{\{1,2,3\}} < \beta_1$

$p_{\{1,2\}} = 0.1364$ $\quad H_{\{1,2\}}$ $\quad p_{\{1,3\}} = 0.0098$ $\quad H_{\{1,3\}}$ $\quad H_{\{2,3\}}$ $\quad p_{\{2,3\}} = 0.0098$

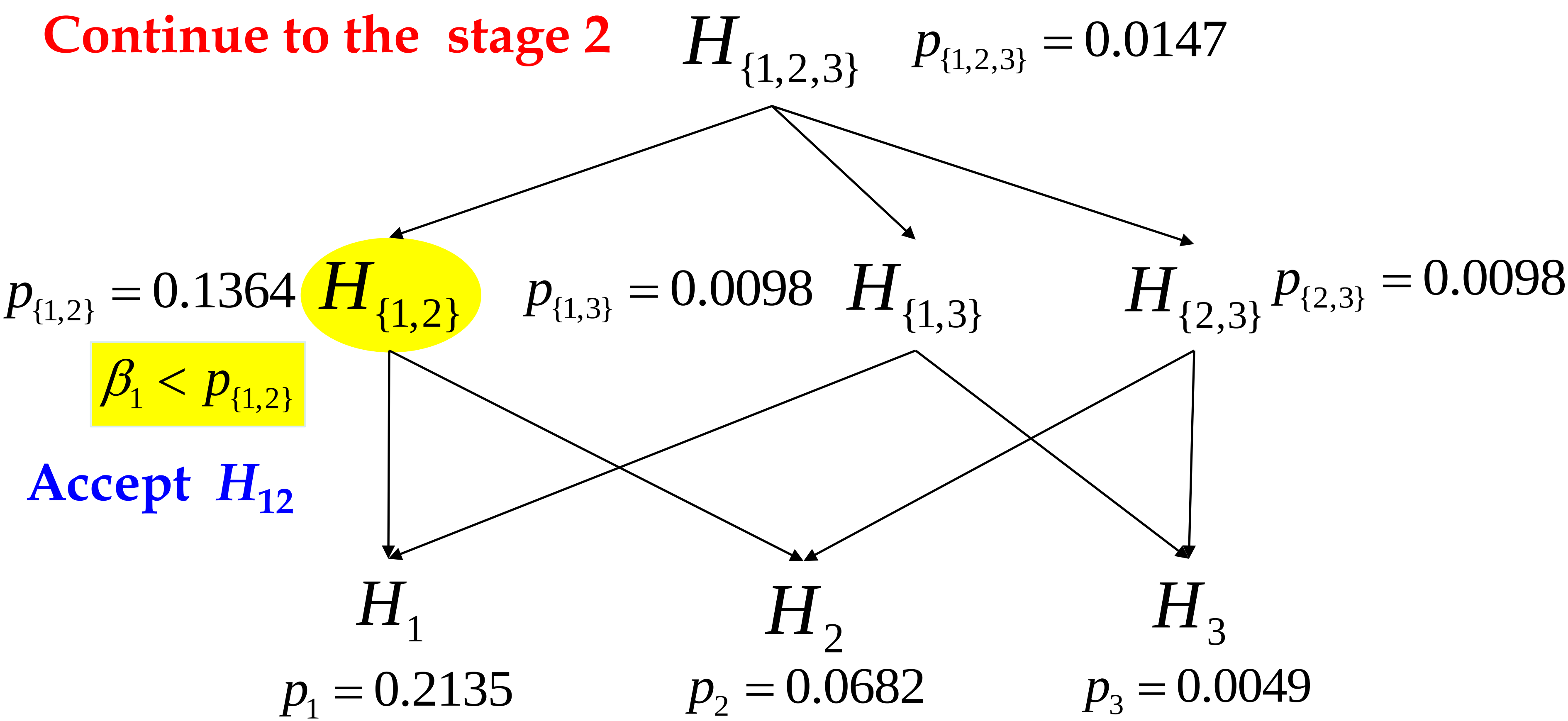
H_1 $\quad H_2$ $\quad H_3$

$p_1 = 0.2135$ $\quad p_2 = 0.0682$ $\quad p_3 = 0.0049$

Step 4

Stopping boudaries

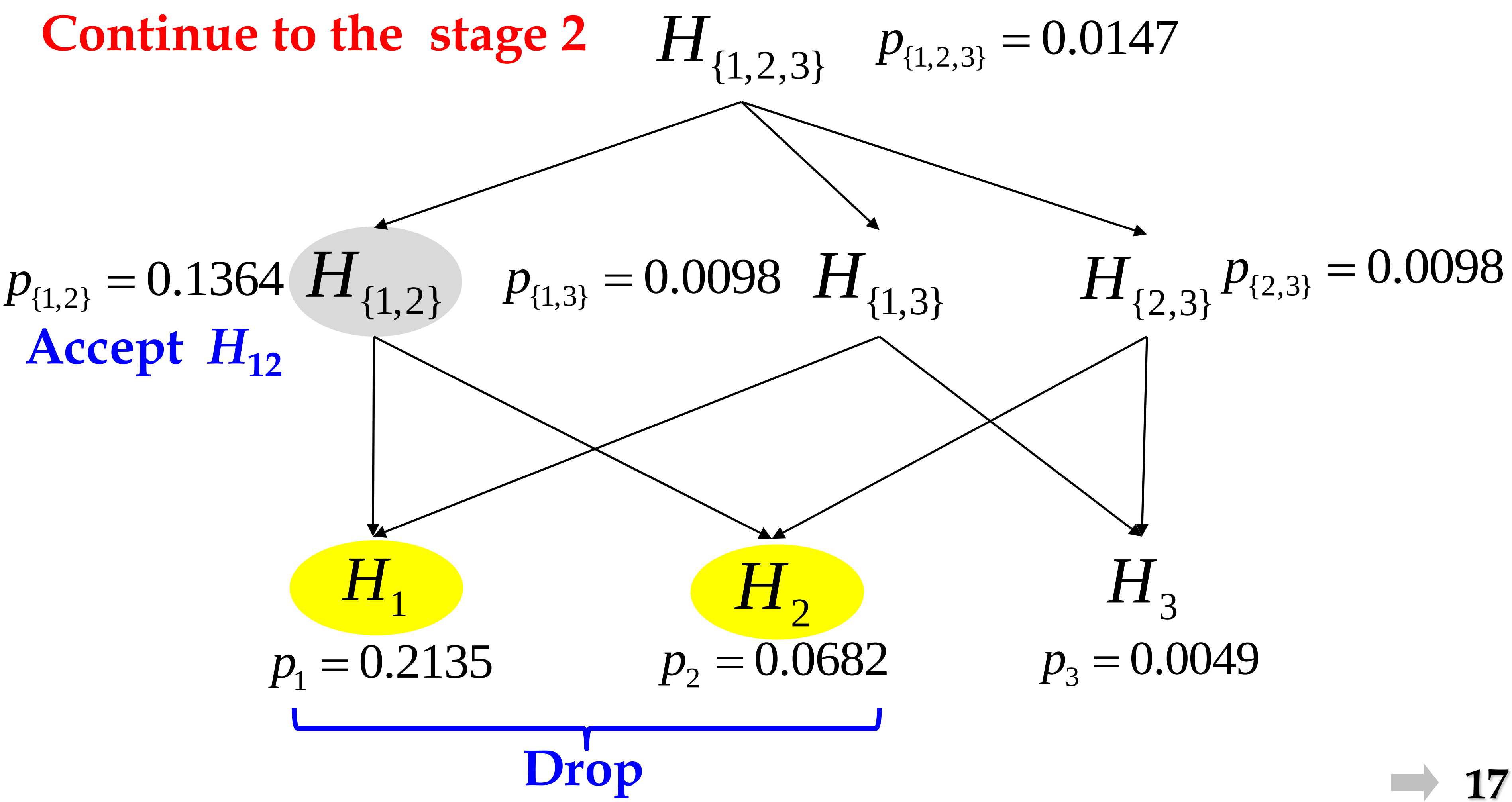
$\alpha_1 = 0.0054, \quad \beta_1 = 0.1, \quad c = 0.0359$ for $\alpha = 0.025$



Step 5

Stopping boudaries

$\alpha_1 = 0.0054, \quad \beta_1 = 0.1, \quad c = 0.0359$ for $\alpha = 0.025$



Step 6

Stopping boudaries

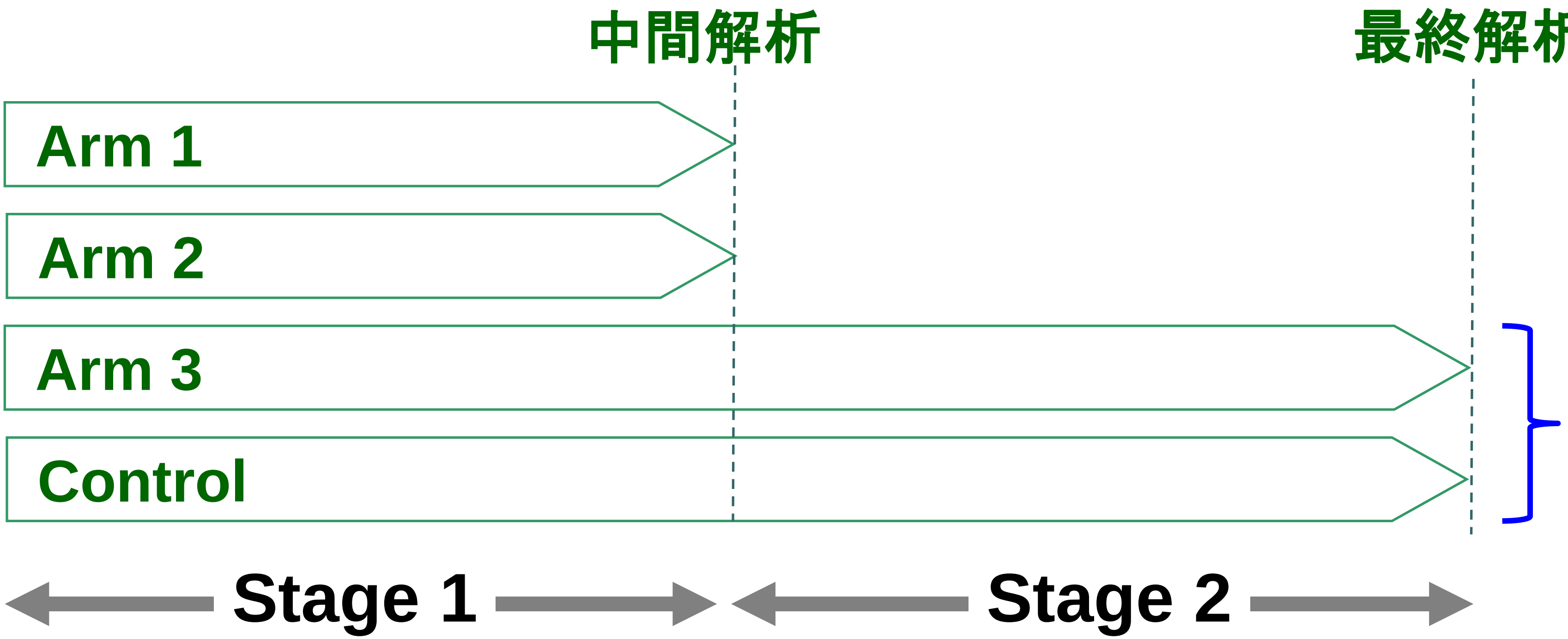
$\alpha_1 = 0.0054, \quad \beta_1 = 0.1, \quad c = 0.0359$ for $\alpha = 0.025$

Continue to the stage 2

$$
\begin{tikzcd}
 & H_{\{1,2,3\}} \quad p_{\{1,2,3\}} = 0.0147 \arrow[dl] \arrow[dr] & \\
p_{\{1,3\}} = 0.0098 \quad H_{\{1,3\}} \arrow[dr] & & H_{\{2,3\}} \quad p_{\{2,3\}} = 0.0098 \arrow[dl] \\
 & H_3 &
\end{tikzcd}
$$

$p_3 = 0.0049$

Case study: 最終解析における閉手順



最終解析の結果

i	Observed mean value	Unadjusted p-value
0	0	-
3	1.9	0.0296

H_3

$p_3 = 0.0296$

Step 7

$H_{\{1,2,3\}}$ $p_{1,\{1,2,3\}} = 0.0147$

$H_{\{1,3\}}$ $p_{1,\{1,3\}} = 0.0098$

$H_{\{2,3\}}$ $p_{1,\{2,3\}} = 0.0098$

H_3 $p_{2,3} = 0.0296$

H_3 $p_{1,3} = 0.0049$

Stage 1

Stage 2

$C\{p_{1,I}, p_{2,3}\}$

Reject H_3

Inverse normal combination test

$$C\{p_{1,\{1,2,3\}}, p_{2,3}\} < c, C\{p_{1,\{1,3\}}, p_{2,3}\} < c,$$

$$C\{p_{1,\{2,3\}}, p_{2,3}\} < c, C\{p_{1,3}, p_{2,3}\} < c$$

$w_1 = w_2 = \sqrt{1/2}$