

# Threshold Sample Enrichment Approach with Heterogeneous Populations in a Clinical Trial for Preeclampsia

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- Fixed-size procedure
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# Heterogeneity in clinical trials

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- With much advancement in science in understanding the disease, various drugs have been put on market and it has become difficult to show large improvement from patients being treated with a new drug.
- To demonstrate an often small improvement, a clinical trial usually enrolls a large number of patients, and thus introduces heterogeneity in patients' improvement over the standard drug treatment.

# Heterogeneity in clinical trials

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- Analysis of data from such a trial often shows that treatment improvement is larger in certain group of patients than in other groups.
- Gordon et al. (2004) reported long-term survival benefit of a randomized clinical trial in which women with ovarian cancer were treated with either pegylated liposomal doxorubicin or topotecan.

# Heterogeneity in clinical trials

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- Overall, 18% reduction in risk of death was observed. Hazard ratio=1.216,  $P = 0.025$ .
- Among patients with platinum sensitive disease, 30% reduction. Hazard ratio=1.432,  $P = 0.00855$ .
- Among patients with platinum-refractory disease, no significance: Hazard ratio=1.069,  $P = 0.31$ .

# Heterogeneity in clinical trials

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- **The big question:** If even before a trial starts, we have good reasons to believe that patients in one group ( $X$ ) will reveal better treatment outcomes than another group ( $Y$ ), then should we consider this information when designing the trial? If yes, then how?
- **A known prior:** If treatment does not look promising for patients in group  $X$ , then very unlikely it will show promising results for patients in group  $Y$ .

# Heterogeneity in clinical trials

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- **Two-stage sample-enrichment strategy:**  
At 1st stage, only patients from group  $X$  are enrolled and randomized.
- Only if the observed difference is promising, will patients from both groups be further enrolled and randomized.
- **Cost-effectiveness:** When the treatment shows no improvement within any groups, the trial has a good chance to stop at the first stage.

# Fixed size procedure

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- $X \sim N(\mu_X, 1)$ ,  $Y \sim N(\mu_Y, 1)$ .
- $\mu_X$  and  $\mu_Y$  measure the treatment difference between the experimental treatment arm and the standard treatment arm for the two subpopulations.
- $H_0 : \mu_X = 0$  and  $\mu_Y = 0$   
versus one-sided alternative hypothesis  
 $H_1 : \mu_X > 0$  or  $\mu_Y > 0$ .

# Fixed size procedure

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- $X_1, \dots, X_n$  from  $N(\mu_X, 1)$  and  $Y_1, \dots, Y_m$  from  $N(\mu_Y, 1)$ .
- Reject  $H_0$  if  $\sqrt{n}\hat{\mu}_X > c_X$  or  $\sqrt{m}\hat{\mu}_Y > c_Y$ .
- $\hat{\mu}_X = \sum_{i=1}^n X_i/n$  and  $\hat{\mu}_Y = \sum_{j=1}^m Y_j/m$ .
- Critical values  $c_X$  and  $c_Y$  are chosen so that

$$\begin{aligned}\alpha &= P_{H_0}\{\sqrt{n}\hat{\mu}_X > c_X, \text{ or } \sqrt{m}\hat{\mu}_Y > c_Y\} \\ &= P_{H_0}\{\sqrt{n}\hat{\mu}_X > c_X\} + P_{H_0}\{\sqrt{m}\hat{\mu}_Y > c_Y\} \\ &\quad - P_{H_0}\{\sqrt{n}\hat{\mu}_X > c_X\}P_{H_0}\{\sqrt{m}\hat{\mu}_Y > c_Y\} \\ &= \alpha_X + \alpha_Y - \alpha_X\alpha_Y.\end{aligned}$$

# Fixed size procedure

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- $\alpha_X = P_{H_0} \{ \sqrt{n} \hat{\mu}_X > c_X \} = \bar{\Phi}(c_X)$  and  
 $\alpha_Y = P_{H_0} \{ \sqrt{n} \hat{\mu}_Y > c_Y \} = \bar{\Phi}(c_Y)$ .
- $c_X = \Phi^{-1}(1 - \alpha_X)$  and  $c_Y = \Phi^{-1}(1 - \alpha_Y)$ .
- **Setting  $\alpha_X = \alpha_Y$ , we have**  
 $\alpha_X = \alpha_Y = 1 - \sqrt{1 - \alpha}$ ,  
 $c_X = c_Y = \Phi^{-1}(\sqrt{1 - \alpha})$ .
- **Power of the test**

$$\beta(\mu_X, \mu_Y; n, m) = \bar{\Phi}(c_X - \sqrt{n}\mu_X) + \bar{\Phi}(c_Y - \sqrt{m}\mu_Y) - \bar{\Phi}(c_X - \sqrt{n}\mu_X) \bar{\Phi}(c_Y - \sqrt{m}\mu_Y).$$

# Sample-enrichment approach

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- Two subpopulations,  $X \sim N(\mu_X, 1)$  and  $Y \sim N(\mu_Y, 1)$ .
- **Key assumption:**  $\mu_X \geq \mu_Y$ .
- First stage, collect  $X_1, \dots, X_{n_1}$  from  $N(\mu_X, 1)$ .
- If  $\sqrt{n_1} \hat{\mu}_{1X} = \sum_{i=1}^{n_1} X_i / \sqrt{n_1} \leq c$ , terminate the trial. No treatment difference.
- Otherwise, continue to observe  $X_{n_1+1}, \dots, X_n$  from  $N(\mu_X, 1)$  and  $Y_1, \dots, Y_m$  from  $N(\mu_Y, 1)$ .
- Reject  $H_0$  if  $\sqrt{n} \hat{\mu}_X > c_X$  or  $\sqrt{m} \hat{\mu}_Y > c_Y$ .

# Sample-enrichment approach

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- Type I error  $\alpha =$

$$\begin{aligned}
 & P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c, \text{ and } \{ \sqrt{n} \hat{\mu}_X > c_X, \text{ or } \sqrt{m} \hat{\mu}_Y > c_Y \} \} \\
 = & P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c, \sqrt{n} \hat{\mu}_X > c_X \} \\
 & + P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c, \sqrt{m} \hat{\mu}_Y > c_Y \} \\
 & - P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c, \sqrt{n} \hat{\mu}_X > c_X, \sqrt{m} \hat{\mu}_Y > c_Y \} \\
 = & P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c, \sqrt{n} \hat{\mu}_X > c_X \} \\
 & + P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c \} P_{H_0} \{ \sqrt{m} \hat{\mu}_Y > c_Y \} \\
 & - P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c, \sqrt{n} \hat{\mu}_X > c_X \} P_{H_0} \{ \sqrt{m} \hat{\mu}_Y > c_Y \} \\
 = & \alpha_X + \alpha_Y - \alpha_X \alpha_Y / \bar{\Phi}(c),
 \end{aligned}$$

# Sample-enrichment approach

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- $\alpha_X = P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c, \sqrt{n} \hat{\mu}_X > c_X \},$   
 $\alpha_Y = P_{H_0} \{ \sqrt{n_1} \hat{\mu}_{1X} > c, \sqrt{m} \hat{\mu}_Y > c_Y \}.$
- $\alpha_X = \frac{\alpha - \alpha_Y}{1 - \alpha_Y / \bar{\Phi}(c)}.$
- $\alpha_X$  and  $\alpha_Y$ —type I error rate for testing group-specific null hypothesis under the sample-enrichment design.
- Setting  $\alpha_X = \alpha_Y$ , then,

$$\alpha_X = \alpha_Y = \bar{\Phi}(c) - \sqrt{\bar{\Phi}^2(c) - \alpha \bar{\Phi}(c)}.$$

# Sample-enrichment approach

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- Power  $\beta(\mu_X, \mu_Y; n, m) =$

$$\begin{aligned} & \Phi(c_Y - \sqrt{m}\mu_Y) \times \\ & \int_{c - \sqrt{n_1}\mu_X}^{\infty} \bar{\Phi}\left(\frac{c_X - \kappa\sqrt{n}\mu_X - \sqrt{\kappa}w}{\sqrt{1 - \kappa}}\right) \phi(w) dw \\ & + \bar{\Phi}(c - \sqrt{\kappa n}\mu_X) \bar{\Phi}(c_Y - \sqrt{m}\mu_Y). \end{aligned}$$

- $\kappa = n_1/n$ .

# Sample-enrichment approach

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## Choose threshold $c$ :

- $\sqrt{n_1}\hat{\mu}_{1X} > c \Rightarrow \hat{\mu}_{1X} > c/\sqrt{n_1}$ .
- Setting  $c/\sqrt{n_1}$  to be the smallest meaningful treatment difference, or a proportion of it.
- Setting  $\gamma (> \alpha)$  so that
$$P_{H_0} \{ \sqrt{n_1}\hat{\mu}_{1X} > c \} = \bar{\Phi}(c) \leq \gamma.$$

# Sample-enrichment approach

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- To compute the critical values  $c_X$  and  $c_Y$ :

$$\alpha_Y = \bar{\Phi}(c) \bar{\Phi}(c_Y),$$
$$\alpha_X = \int_c^\infty \bar{\Phi}\left(\frac{c_X - \sqrt{\kappa}W}{\sqrt{1-\kappa}}\right) \phi(w) dw.$$

- Thus

$$c_Y = \Phi^{-1}\left(1 - \alpha_Y / \bar{\Phi}(c)\right).$$

- Find the value of  $c_X$  via numerical integration.

# Sample-enrichment approach

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## Testing Overall Treatment Effect

- $\mu = \pi\mu_X + (1 - \pi)\mu_Y$ ,  $0 < \pi < 1$ .
- $H_0 : \mu = 0$  versus  $H_1 : \mu > 0$ .
- With  $\hat{\mu} = \pi\hat{\mu}_X + (1 - \pi)\hat{\mu}_Y$ , reject  $H_0$  if

$$\hat{\mu} / \sqrt{\frac{\pi^2}{n} + \frac{(1 - \pi)^2}{m}} > \Phi^{-1}(1 - \alpha).$$

- Power  $\beta(\mu_X, \mu_Y; n, m)$

$$= \bar{\Phi} \left( Z_{1-\alpha} - \mu / \sqrt{\frac{\pi^2}{n} + \frac{(1 - \pi)^2}{m}} \right).$$

# Sample-enrichment approach

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For the two-stage enrichment design, stop if

$$\sqrt{n_1} \hat{\mu}_{1X} \leq c_0.$$

- If  $\sqrt{n_1} \hat{\mu}_{1X} > c_0$ , then move to 2nd stage and reject  $H_0$  if

$$\hat{\mu} / \sqrt{\frac{\pi^2}{n} + \frac{(1-\pi)^2}{m}} > C.$$

- Power =  $\beta(\mu_X, \mu_Y; n, m)$

$$= \int_{c_0 - \sqrt{n_1} \mu_X}^{\infty} \phi(w) \bar{\Phi} \left( \frac{C \sqrt{\frac{\pi^2}{n} + \frac{(1-\pi)^2}{m}} - \mu - \pi w \sqrt{\frac{\kappa}{n}}}{\sqrt{\frac{(1-\kappa)\pi^2}{n} + \frac{(1-\pi)^2}{m}}} \right) dw$$

# Sample-enrichment approach

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- Type I error =  $\alpha(\mu_X; n, m) =$

$$\int_{c_0 - \sqrt{n_1} \mu_X}^{\infty} \phi(w) \bar{\Phi} \left( \frac{C \sqrt{\frac{\pi^2}{n} + \frac{(1-\pi)^2}{m}} - \pi w \sqrt{\frac{\kappa}{n}}}{\sqrt{\frac{(1-\kappa)\pi^2}{n} + \frac{(1-\pi)^2}{m}}} \right) dw.$$

- Power depends on both  $\mu_X$  and  $\mu_Y$ .
- Type I error depends on  $\mu_X$ .
- Choose  $c_0, C$  that

$$\sup_{\mu_X} \alpha(\mu_X; n, m) \leq \alpha.$$

# The CPEP trial

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- Preeclampsia is a hypertensive disorder that occurs only in women during pregnancy.
- Potential risk: eclampsia, strokes, pulmonary edema, renal failure, liver dysfunction, liver rupture, coagulopathy, hemolysis, placental abruption.
- A major focus in obstetrical research to effectively prevent preeclampsia.

# The CPEP trial

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- The CPEP (Calcium to Prevent Preeclampsia) trial at NICHD (1992-1995) to investigate the effects of calcium supplementation to prevent preeclampsia.
- Treatment: 2g of elemental calcium daily or placebo.
- Investigators expecting 50% reduction in preeclampsia incidence.

# The CPEP trial

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- 4589 healthy women who were 13 to 21 weeks pregnant were equally randomized to calcium ( $n = 2295$ ) or placebo ( $n = 2294$ ).
- Excluding 296 women due to missing preeclampsia status, the study yielded 2143 women in calcium group and 2150 in placebo group.

# The CPEP trial

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- 158 preeclampsia cases (7.37%) in calcium group.
- 168 preeclampsia cases (7.81%) in placebo group.
- Only 5% reduction in preeclampsia incidence.
- No effect of calcium ( $P$ -value=0.6).

# The CPEP trial

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- Prior to enrollment, some women had low calcium intake, some had high intake.
- **It is believed that, if calcium supplementation indeed can help prevent preeclampsia, then the reduction in preeclampsia incidence is expected to be higher among the healthy nulliparae who normally have low calcium intake than among those who normally have high calcium intake.**

# The CPEP trial

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- The CPEP trial data well support this assumption.
- Preeclampsia incidence by treatment and prior calcium intake:

	Low intake			High intake		
	PE-free	PE	% inci.	PE-free	PE	% inci.
Calcium	1052	86	7.56	933	72	7.16
Placebo	1009	92	8.36	973	76	7.24

- Nearly 10% reduction among low calcium intake group ( $X$ ). Only 1% reduction among high calcium intake group ( $Y$ ).

# The CPEP trial

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**This information, however, was not considered at the time the CPEP trial was designed. Had this information been used to design the trial as a two-stage sample-enrichment trial, the trial could have been terminated with much fewer enrollments, and thus could have saved substantial resources.**

# The CPEP trial

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- 1st stage only enrolled  $n_1$  women who had reported low calcium intake in the past 24 hours.
- These  $n_1$  women were then subsequently equally randomized to receive either calcium supplementation or placebo.

# The CPEP trial

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- If the observed percent reduction in preeclampsia incidence rate is larger than 25%, then the trial would be expanded to women who reported high calcium intake 24 hours prior to enrollment.
- Otherwise the study would be terminated without further enrollment.
- Claim calcium supplementation is of no help in reducing preeclampsia incidence.

# The CPEP trial

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- For various choices of  $n_1$ , the percent reduction in preeclampsia incidence rate of calcium supplementation from placebo is estimated. Inclusion of women into the analysis is based on their enrollment date. For example, if  $n_1 = 1000$ , then we select the first 1000 women enrolled into the study who reported low calcium intake 24 hours prior to the enrollment.

# The CPEP trial

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- % reduction in preeclampsia incidence among women who reported higher prior calcium intake in the CPEP trial

	$n_1$					
	1000	1100	1200	1300	1400	1500
% reduc.	12.5	9.42	5.82	11	13.69	6.17

# The CPEP trial

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- For every choice of  $n_1$ , the observed percent reduction in preeclampsia incidence rate by calcium supplementation is substantially less than the 25% threshold, and much smaller than the expected 50% reduction.
- The percent reduction is expected to be even smaller among women who reported high calcium intake in the past 24 hours.

# The CPEP trial

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- Therefore, if the sample-enrichment design were used, the trial would be terminated after the first stage without further enrollment.

# Summary

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- The sample-enrichment design strategy answers cost and ethical concerns.
- Relies on the key assumption that certain patients can benefit more than others from the treatment.
- Rapid growing research in genome-wide association studies and the search for disease-associated biomarkers may provide sound justification for patients heterogeneity.

# Summary

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- Adaptive in nature in the sense that the inclusion criteria of patients are modified after the first stage to expand targeted patients population.
- The first stage data can also be used to modify other design features of the trial.

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