Sample size calculation and optimal design for univariate and multivariate regression-based norming

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ITC 2024 - Granada

Outline

1. Introduction
2. Research question
3. Optimal design
4. Sample size calculation
5. Extensions to multivariate norming
6. Current and future work

Research question

To prevent mistakes in the assessment of individuals, **norms should be precise**, that is, not being strongly affected by sampling error in the sample on which the norms are based.
How to **minimize sampling error** and **maximize precision** of the norms?

1. Adopt an efficient approach to norming ⇒ **continuous norming**
2. Find a sample composition (e.g. which age groups to include) that maximizes precision of estimation of the norms ⇒ the **optimal design**
3. Take a sufficiently large sample for the normative study ⇒ **sample size calculation formulas**

Continuous norming methods

- **Inferential norming:** Angoff and Robertson [1987]; Zachary and Gorsuch [1985]; Zhu and Chen [2011]
- **Regression-based norming**
  - Multiple linear regression (MLR): Oosterhuis et al. [2016]; Van Breukelen and Vlaeyen [2005]; Van der Elst et al. [2011, 2005, 2006]
  - GAMLSS: Timmerman et al. [2021]; Voncken et al. [019a,b]
- **Semi-parametric norming**
  - Quantile regression: Crompvoets et al. [2021]; Sherwood et al. [2015]; Vaughan et al. [2016]
  - cNORM: Gary et al. [2023]; Lenhard et al. [2019, 2018]

MLR-based norming

1. Fit $\mathbf{y} = \mathbf{X}\beta + \epsilon$, with $\epsilon \sim N(0, \sigma^2)$, thus obtaining $\hat{\beta}$ and $\hat{\sigma}$ from the normative sample

2. To compare **a new individual** with the reference population:
    - Compute Z-score: $\hat{Z}_0 = \frac{Y_0 - \hat{Y}_0}{\hat{\sigma}} = \frac{Y_0 - \mathbf{x}_0^T \hat{\beta}}{\hat{\sigma}}$
    - Compute PR-score: $\hat{PR}_0 = \Phi\left(\hat{Z}_0\right) \times 100$

$\mathbf{x}_0$ = individual's scores on the predictors, $\Phi(.)$ = cdf of the standard normal distribution

- Simple and common approach (see delCacho Tena et al. [2024])
- **Limitations**: Normality & Homoscedasticity

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Optimal design: Theory

- What is a design?

  Joint distribution of the norm predictors in the sample given the sample size (N), e.g. sex distribution and age distribution per sex level in the sample

- What is the **Optimal Design** (OD)?

  The joint distribution of the norm predictors in the sample that **minimizes** the sampling variance of the norm statistic (e.g. Z-score, PR-score) given N

- Innocenti et al. [023a]: **OD** is obtained by **minimizing the maximum of the sampling variance** of Z-score and PR-score over all possible combinations of the levels of the norm predictors, given N.

Optimal design: Results

Let $\epsilon_i \sim N\left(0, \sigma^2\right)$

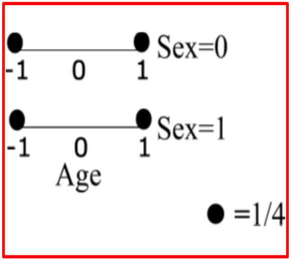
$$Y_i = \beta_0 + \beta_1 Age_i + \beta_2 Sex_i + \epsilon_i \tag{1}$$

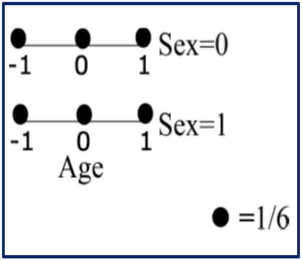
$$Y_i = \beta_0 + \beta_1 Age_i + \beta_2 Sex_i + \beta_3 Age_i^2 + \epsilon_i \tag{2}$$

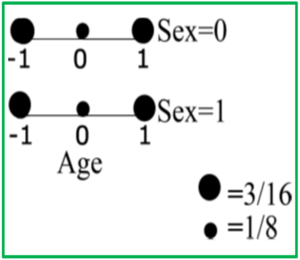
$$Y_i = \beta_0 + \beta_1 Age_i + \beta_2 Sex_i + \beta_4 Age_i Sex_i + \epsilon_i \tag{3}$$

$$Y_i = \beta_0 + \beta_1 Age_i + \beta_2 Sex_i + \beta_3 Age_i^2 + \beta_4 Age_i Sex_i + \epsilon_i \tag{4}$$

$$Y_i = \beta_0 + \beta_1 Age_i + \beta_2 Sex_i + \beta_3 Age_i^2 + \beta_4 Age_i Sex_i + \beta_5 Age_i^2 Sex_i + \epsilon_i \tag{5}$$



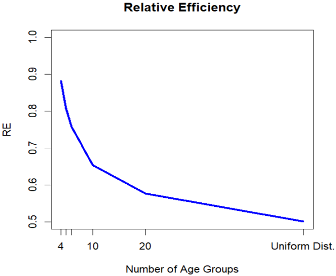


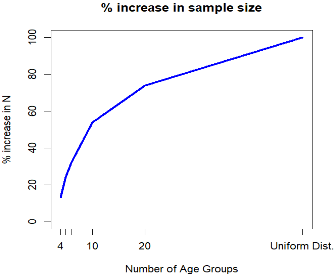


Why so few age groups under OD?

The 2/3 age groups required by OD follow from assuming a linear/quadratic age effect. **If this assumption is correct, including additional age groups yields a loss of statistical efficiency**. E.g.:

$$Y_i = \beta_0 + \beta_1 Age_i + \beta_2 Sex_i + \beta_3 Age_i^2 + \epsilon_i$$





Relative Efficiency (RE): ratio of sampling variance under OD to sampling variance under non-OD

% increase in sample size relative to OD: $\left(RE^{-1} - 1\right) 100\%$

Sample size calculation for MLR-based norming

- Sample size requirements based on simulations in Oosterhuis et al. [2016], but limited to two norm predictors only
- Innocenti et al. [023a] Sample size formulas for Z-score and PR-score **under OD** and any number of norm predictors
  - **Power:**
    - Norms application = **classification problem**, which can be expressed as: H_0 : "average" performance vs H_1 : "below average" performance given a chosen cut-off for classification
    - N^* = **to detect the smallest clinically relevant difference** between subject's norm value and the cut-off for classification, given pre-specified Type I error rate and statistical power
  - **Precision:** N^* = **half** the confidence interval **width equals** the pre-specified **margin of error**
  - Formulas based on delta method, which a simulation study has shown to be accurate for $N > 300$ for Z-scores and $N > 1600$ for PR-scores. Accurate = relative bias $< 5\%$

Application (1/2)

1. **Choose a norming model**

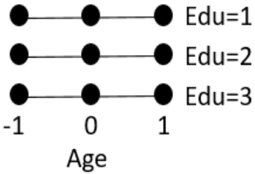
   Van der Elst et al. (2006):

   $$\text{Letter M naming}_i = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Low\ Edu + \beta_4 High\ Edu + \epsilon_i$$

   $$\epsilon_i \sim N\left(0, \sigma^2\right)$$

2. **Find the OD**

9 age-education combinations of equal weight



3. **Choose the norm statistic**

   Z-score $= -1.64$ (chosen cut-off for classification)

Application (2/2)

4 **Sample size calculation**

- **Power:** $H_0 : Z = -1.64$ vs $H_1 : Z < -1.64$, Effect Size $(ES) = 0.36$ (distance between 10th and 5th percentiles), $\alpha = 5\%$ and Power $= 80\%$

$$N^* = \left[\frac{z_{1-\alpha}\left(k+1+\frac{Z_c^2}{2}\right)^{1/2} + z_{1-\beta}\left(k+1+\frac{(Z_c-ES)^2}{2}\right)^{1/2}}{ES} \right]^2 = \left[\frac{1.64\left(4+1+\frac{1.64^2}{2}\right)^{1/2} + 0.84\left(4+1+\frac{(-1.64-0.36)^2}{2}\right)^{1/2}}{0.36} \right]^2 \approx 314$$

  35 subjects for each age-education combination of OD

- **Precision:** confidence level $1-\alpha = 0.95$, margin of error $(MoE) = 0.18$ (half distance between 10th and 5th percentiles)

$$N^* = \left[\frac{z_{1-\alpha/2}\left(k+1+\frac{Z_0^2}{2}\right)^{1/2}}{MoE} \right]^2 = \left[\frac{1.96\left(4+1+\frac{1.64^2}{2}\right)^{1/2}}{0.18} \right]^2 \approx 753$$

  84 subjects for each age-education combination of OD

Sample size formulas implemented in R functions

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Multivariate norming (1/3)

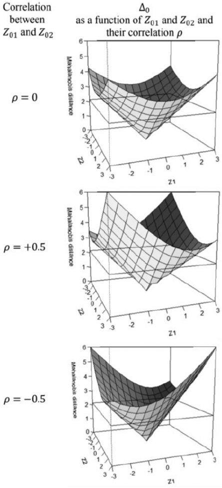
- Often normative studies derive norms for multiple tests with the same sample
- Univariate approach for each test is simpler but
  - Does **not take into account correlation** between test scores of the same subject -> **Incorrect classification** of subjects in clinical practice (see Agelink van Rentergem et al. [2019]; Su et al. [2015])
  - Multiple testing issues
- Current multivariate approaches
  - Van der Elst et al. [2017]: Same steps as MLR-based approach but using **multivariate multiple linear regression** -> What is the **multivariate performance** of a testee?
  - Agelink van Rentergem et al. [2018, 2019, 2017]
    - Advanced Neuropsychological Diagnostics Infrastructure (de Vent et al. [2016])
    - **Multilevel multivariate regression**
    - Multivariate performance summarized with **Hotelling's** T^2 (Huizenga et al. [2007])

Multivariate norming (2/3)

- Innocenti et al. [023b]:
  1. Multivariate multiple linear regression: $\mathbf{Y} = \mathbf{XB} + \mathbf{E}$, with $\mathbf{E} \sim N(\mathbf{0}, \Sigma)$
  2. Multivariate performance summarized with Mahalanobis Distance (MD):

$$\hat{\Delta}_0 = \sqrt{\left(\mathbf{y}_0 - \hat{\mathbf{y}}_0\right)' \left(\hat{\Sigma}\right)^{-1} \left(\mathbf{y}_0 - \hat{\mathbf{y}}_0\right)}$$

- MD $=$ multivariate Z-score vs Hotelling's T^2 $=$ multivariate t-statistic: Small differences in large samples, but MD made the derivation of OD easier
- **Limitations** (shared with Van der Elst and Ageling van Rentergem's approaches): Multivariate normality & homoscedasticity



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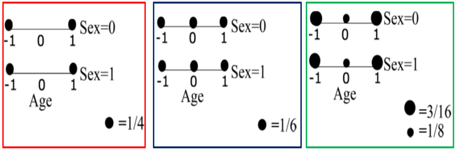
Multivariate norming (3/3)

Sampling variance of MD similar to sampling variance of Z-score under univariate norming:

- **Same OD as the univariate case**



- **Sample size formulas similar to those for Z-score under the univariate case**, also implemented in R functions

- Sample size formulas based on delta method, which a simulation study has shown to be accurate if $N > 300$ and $MD > 1.18$ (median of χ^2 distribution with df=2). Accurate = relative bias$< 5\%$, simulations limited to bivariate case.

Current work

with Dr. Alberto Cassese, University of Florence (IT)

- Sample size calculation for non-optimal designs
- Extensions of OD to models with 3 predictors (e.g. age, sex, education)
- Shiny Apps for sample size formulas
- Sample size calculation for interval estimation with assurance probability
- Simulation studies to assess accuracy of formulas for multivariate approach

Future work

- Sample size calculations and OD for most promising continuous norming approaches:
    - GAMLSS
    - cNORM
- Efficient designs that are robust against model misspecification at the design stage

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Thank you for your attention!

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Appendix

Sampling variances for univariate norming

- Based on the delta method:

$$V\left(\hat{Z}_0\right) \approx \frac{d\left(\mathbf{X},\xi\right)}{N} + \frac{Z_0^2}{2\left(N-k-1\right)}$$

$$V\left(\hat{PR}_0\right) \approx V\left(\hat{Z}_0\right) \times \left(100 \times \phi\left(Z_0\right)\right)^2$$

where

$$d\left(\mathbf{X},\xi\right) = N\sigma^{-2}V\left(\hat{Y}_0\right) = N\mathbf{x}_0^T\left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{x}_0$$

is the **standardized prediction variance**, ξ is the design of the normative sample, k = number of predictors, $\phi(.)$ is the pdf of the standard normal distribution, and $\mathbf{x}_0$ is the vector of the new individual's scores on the predictors.

- Simulation study: for $N \geq 300$ relative bias of $V\left(\hat{Z}_0\right) \in (-3\%, +3\%)$; for $N \geq 1600$ relative bias of $V\left(\hat{PR}_0\right) \in (-5\%, +5\%)$

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Sample size calculation: Power

1. Choose: (i) the model for norming with k predictors, (ii) the cut-off point for decision making (Z_c or PR_c) , (iii) the smallest clinically relevant difference δ between subject's norm value (Z_t or PR_t) and the cut-off point, (iv) the Type I error rate α and statistical power $1-\beta$
2. For Z-scores, the required sample size is

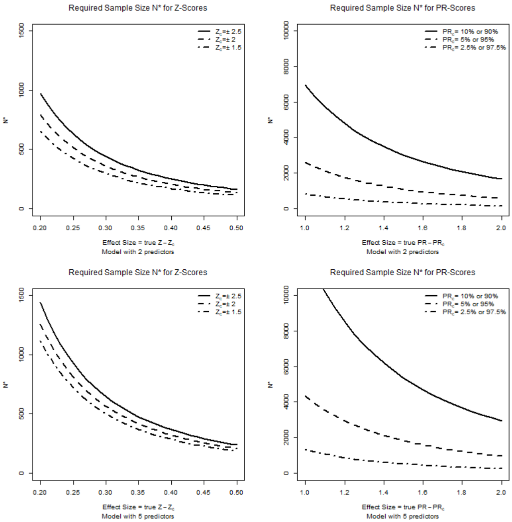
$$N^* = \left[\frac{z_{1-\alpha} \left(k + 1 + \frac{Z_c^2}{2} \right)^{1/2} + z_{1-\beta} \left(k + 1 + \frac{Z_t^2}{2} \right)^{1/2}}{\delta} \right]^2$$

For PR-scores, the required sample size is

$$N^* = \left[\frac{z_{1-\alpha} \cdot 100 \cdot \phi \left(Z_{PR_c} \right) \left(k + 1 + \frac{Z_{PR_c}^2}{2} \right)^{1/2} + z_{1-\beta} \cdot 100 \cdot \phi \left(Z_{PR_t} \right) \left(k + 1 + \frac{Z_{PR_t}^2}{2} \right)^{1/2}}{\delta} \right]^2$$

Sample size calculation: Results

Univariate norming: Type I error rate $= 5\%$, Power $= 80\%$



Sample size calculation: Precision

Alternative approach: N^* = **half the confidence interval width equals the pre-specified margin of error**

1. Choose: (i) the model for norming with k predictors, (ii) the Z-score or PR-score of interest (e.g. $Z_0 = -2$ or $PR_0 = 5\%$) , (iii) the desired margin of error τ, (iv) the confidence level $1 - \alpha$
2. For Z-scores, the required sample size is

$$N^* = \left[\frac{z_{1-\alpha/2} \left(k + 1 + \frac{Z_0^2}{2} \right)^{1/2}}{\tau} \right]^2$$

For PR-scores, the required sample size is

$$N^* = \left[\frac{z_{1-\alpha/2} \cdot 100 \cdot \phi\left(Z_0\right) \cdot \left(k + 1 + \frac{Z_0^2}{2} \right)^{1/2}}{\tau} \right]^2$$

Multivariate norming (1/2)

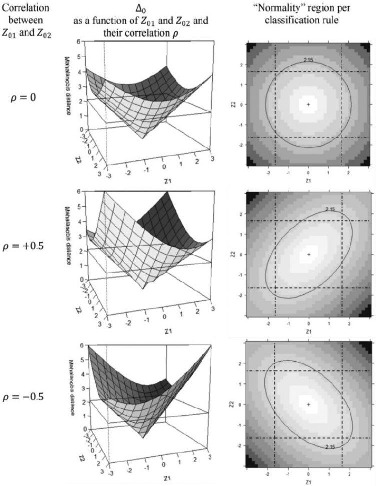
- Innocenti et al. [023b]:
  1. Multivariate multiple linear regression: $\mathbf{Y} = \mathbf{XB} + \mathbf{E}$, with $\mathbf{E} \sim N(\mathbf{0}, \Sigma)$
  2. Multivariate performance summarized with Mahalanobis Distance (MD):

$$\hat{\Delta}_0 = \sqrt{(\mathbf{y}_0 - \hat{\mathbf{y}}_0)' \left(\hat{\Sigma}\right)^{-1} (\mathbf{y}_0 - \hat{\mathbf{y}}_0)}$$

For 2 tests:

$$\hat{\Delta}_0 = \sqrt{\frac{\hat{Z}_{01}^2 + \hat{Z}_{02}^2 - 2\hat{Z}_{01}\hat{Z}_{02}\hat{\rho}}{1 - \hat{\rho}^2}}$$

with $\hat{Z}_{01}$ and $\hat{Z}_{02}$ = Z-scores corresponding to the first and second tests, and $\hat{\rho}$ = correlation between them



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Multivariate norming (2/2)

- Based on the delta method:

$$V\left(\hat{\Delta}_0\right) \approx \frac{d\left(\mathbf{X},\xi\right)}{N} + \frac{\Delta_0^2}{2\left(N-k-1\right)}$$

where

$$d\left(\mathbf{X},\xi\right) = N\sigma^{-2}V\left(\hat{Y}_0\right) = N\mathbf{x}_0^T\left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{x}_0$$

- Simulation study: For 2 outcomes, $N \geq 300$ and $\Delta_0 > 1.18$ relative bias of $V\left(\hat{\Delta}_0\right) \in (-5\%, +5\%)$
- Sample size: Power

$$N^* = \left[\frac{z_{1-\alpha}\left(k+1+\frac{\Delta_c^2}{2}\right)^{1/2} + z_{1-\beta}\left(k+1+\frac{\Delta_t^2}{2}\right)^{1/2}}{ES}\right]^2$$

- Sample size: Precision

$$N^* = \left[\frac{z_{1-\alpha/2}\left(k+1+\frac{\Delta_0^2}{2}\right)^{1/2}}{MoE}\right]^2$$

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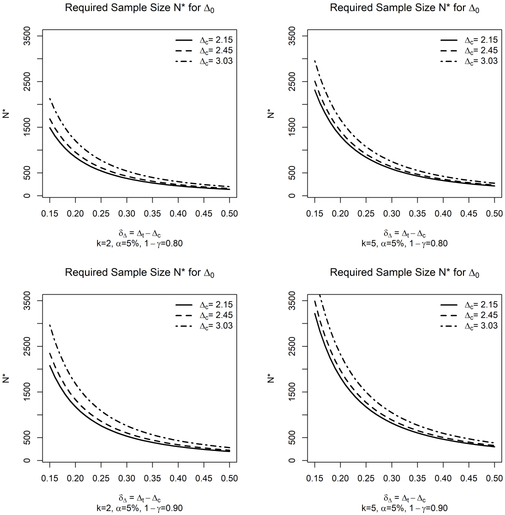
Sample size calculation: Results

Multivariate Norming: 2 outcomes, Type I error rate = 5%, Power = 80%



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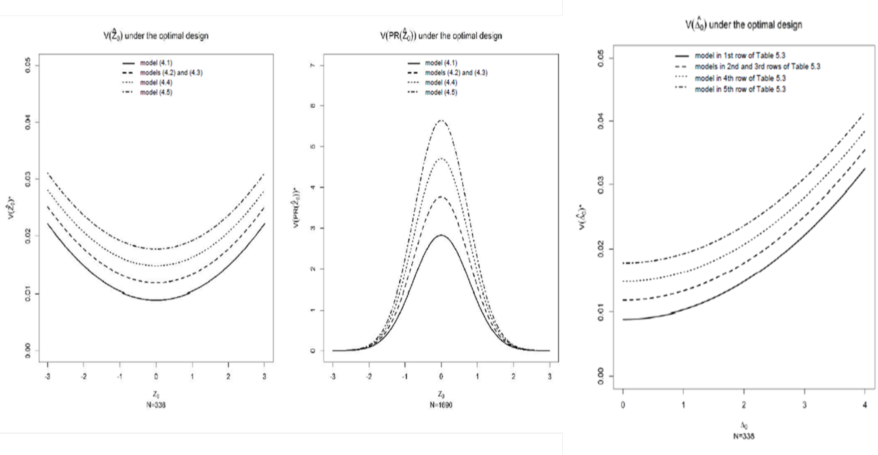
Sampling variances: Figures



Optimal Design: Derivation

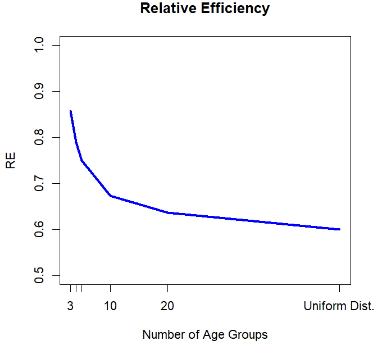
1. $V\left(\hat{Z}_0\right)$, $V\left(\hat{PR_0}\right)$, and $V\left(\hat{\Delta}_0\right)$ depend on ξ only through

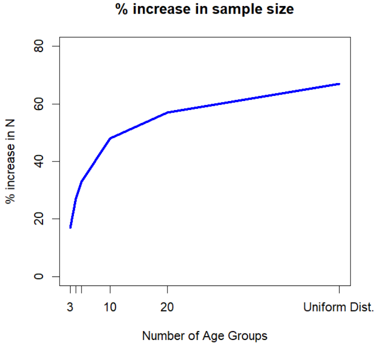
$$d\left(\mathbf{X},\xi\right) = N\sigma^{-2}V\left(\hat{Y}_0\right) = N\mathbf{x}_0^T\left(\mathbf{X}^T\mathbf{X}\right)^{-1}\mathbf{x}_0$$

   so to minimize $V\left(\hat{Z}_0\right)$ and $V\left(\hat{PR_0}\right)$ over the design region, one should minimize $d\left(\mathbf{X},\xi\right)$ over the design region.
2. **G-optimality**: minimize the maximum of $d\left(\mathbf{X},\xi\right)$ over the design region -> optimality criterion for prediction
3. From the Equivalence Theorem (Schwabe [1996]): Under Normality and Homoscedasticity, **G-optimality is equivalent to D-optimality**
4. **D-optimality**: minimize the determinant of $\left(\mathbf{X}^T\mathbf{X}\right)^{-1}$ -> optimality criterion for estimation of regression coefficients
5. Schwabe [1996]: D-optimal designs for multi-factor models can be derived as (Kronecker) product designs of D-optimal designs of one-factor sub-models. Models with no or all possible interactions have the same D-optimal design.

Why so few age groups under OD?

$$Y_i = \beta_0 + \beta_1 Age_i + \beta_2 Sex_i + \epsilon_i$$





Relative Efficiency (RE): ratio of sampling variance under OD to sampling variance under non-OD

% increase in sample size relative to OD: $\left(RE^{-1} - 1\right) 100\%$

Maximin design

- The optimal design depends on the assumed model, but at the design phase there is **uncertainty about the "true" model** (i.e. best fitting polynomial)
- A solution: Find the **most robust** design against misspecification of the model. Two alternative criteria:
  - **Relative Efficiency** (RE): ratio of sampling variance under OD to sampling variance under sub-OD, given N ⇒ **RE maximin design** $=$ highest minimum relative efficiency across all plausible models
  - **Efficiency**: $1/$sampling variance ⇒ **Absolute maximin design** $=$ highest minimum efficiency across all plausible models