Maximin Optimal Cluster Randomized Designs Accounting for Treatment Effect Heterogeneity

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Disclosures

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Introduction

- Cluster randomized trials (CRT): treatment randomized at cluster level; outcomes (typically) collected at individual level
- Heterogeneous treatment effects (HTE): effect modifiers driving variations in a patient's response to interventions

Cluster treatment indicator

$$Y_{ij} = \beta_1 + \beta_2 W_i + \beta_3 X_{ij} + \beta_4 X_{ij} W_i + \gamma_i + \epsilon_{ij} \quad (1)$$

Individual covariate

HTE

- Confirmatory HTE analyses must be pre-specified
  - Little guidance on how to power these analyses when we are uncertain about the outcome ICC, $\rho_{y|x}$, and covariate ICC, ρ_x

cluster size

$$var(\widehat{\beta_4}) = \sigma^2_{HTE} = \frac{\sigma^2_{y|x}(1-\rho_{y|x})\{1+(m+1)\rho_{y|x}\}}{nm\sigma^2_w\sigma^2_x\{1+(m-2)\rho_{y|x}-(m-1)\rho_x\rho_{y|x}\}} \quad (2)$$

clusters

Outcome ICC

Covariate ICC

[Yang et al.,(2020)]

Knowledge Gaps

1. What formulations of cluster size *m* and number of clusters *n* will minimize σ^2_{HTE}, with respect to a budget constraint, when ICCs are known?

2. When ICCs are not known, can we find a (*m*, *n*) design that will be most efficient among scenarios of inefficient ICC combinations?

3. Is there a way to adequately power a CRT for both HTE and average treatment effect (ATE) analyses?

Application to K-DPP Study

Kerala Diabetes Prevention Program [Thankappan et al., 2018]

- CRT of peer-support lifestyle diabetes intervention

- Secondary outcome: change in Indian Diabetes Risk Score
  - Post-hoc HTE: IDRS interaction with BMI

- 60 clusters with 10-23 participants each

KG1: HTE Locally Optimal Design

KG1: What formulations of cluster size *m* and number of clusters *n* will minimize σ^2_{HTE}, with respect to a budget constraint, when ICCs are known?

- Locally optimal design (LOD): design that maximizes power/minimizes variance under budget constraints for fixed values of design parameters

- Budget constraint:

(3)

per-cluster cost

per-subject cost

$$B = cn + smn$$
$$= n(c + sm) \Rightarrow \boxed{n = \frac{B}{c + sm}}$$

Replace *n* in σ^2_{HTE} and minimize for *m*

KG1: HTE Locally Optimal Design

Proposition 1 - Minimizing σ^2_{HTE} with respect to m, the HTE LOD for a given minimum number of clusters, $\underline{n}$, is:

i. If $\frac{\rho_{y|x}(k+1)}{\rho_{y|x}k+1} < \rho_x \leq 1$ and $m_{\text{opt}} \leq \frac{B/\underline{n}-c}{s}$

$$m_{\text{opt}} = \frac{(1-\rho_{y|x})(1-\rho_x) + \sqrt{\rho_{y|x}^{-1}k^{-1}(1-\rho_{y|x})(\rho_x-\rho_{y|x})\{1-(k+2)\rho_{y|x}+k+1)\rho_x\rho_{y|x}\}}}{k^{-1}(\rho_x-\rho_{y|x})-\rho_{y|x}(1-\rho_x)} \quad (4)$$

$$n_{\text{opt}} = \frac{B}{c+sm_{\text{opt}}}$$

Only depends on cost ratio (c/s)

ii. Otherwise

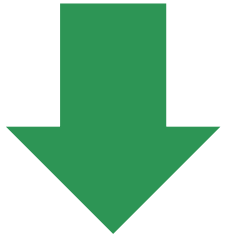
$$m_{opt} = \frac{B/\underline{n}-c}{s}$$

$$n_{\text{opt}} = \frac{B}{c+sm_{\text{opt}}}$$

KG1: Application to K-DPP

- Intervention cluster- to -individual cost ratio $\mathrm{k} \approx 30$
  - Accounting for cheaper control arm, assume $k = 20$ and $B = \$20{,}000$

- $\Delta_{IDRS} = -1.5; \Delta_{HTE} = 0.25 \times \Delta_{IDRS} = -0.375$
- $\rho_{y|x} = 0.028, \rho_x = 0.055$



- If minimum of 66 clusters (maximum *m* of 40):

LOD: $m_{opt} = 40, n_{opt} = 66$

KG2: HTE Maximin Design

- LOD requires fixed/known ICCs – unrealistic expectation

KG2: When ICCs are not known, can we find a (*m*, *n*) design that will be most efficient among scenarios of inefficient ICC combinations?

- Maximin designs (MMD): design that is highly efficient in worst case parameter scenarios [van Breukelen and Candel, 2015]
- Comparing designs (*m*, *n*) based on relative efficiency compared to LOD at a specific $(\rho_{y|x}, \rho_x)$ combination:

$$RE_{\text{HTE}} = \frac{\sigma^{2^*}_{\text{HTE}}}{\sigma^2_{\text{HTE}}}$$

HTE variance under LOD$(\rho_{y|x}, \rho_x)$

HTE variance at (*m*, *n*) and $(\rho_{y|x}, \rho_x)$

KG2: HTE Maximin Design

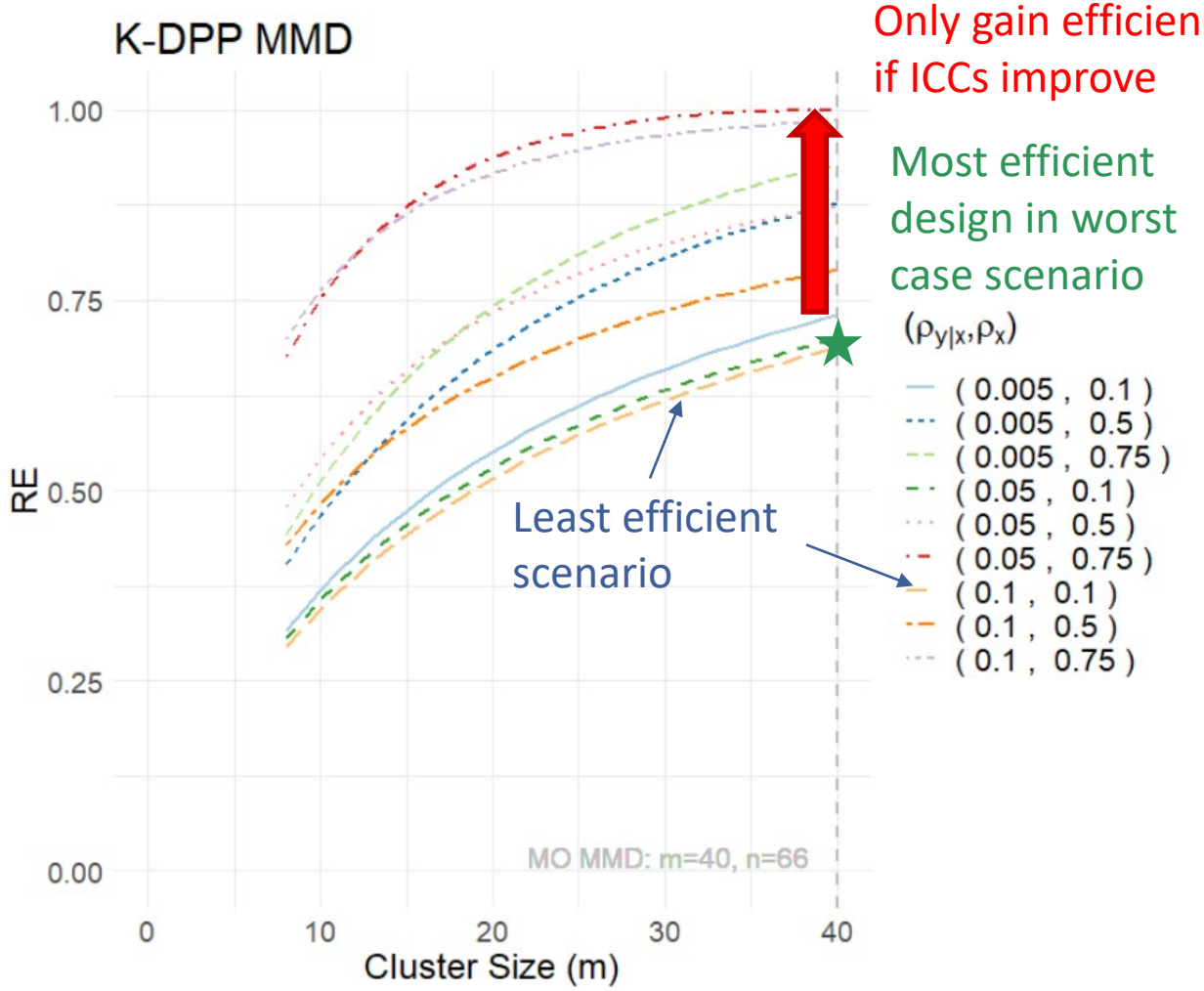
MMD for assessing HTE in CRTs

1. Define the parameter space $(\rho_{y|x}, \rho_x)$and design space $(m, n(m))$
2. For each $(\rho_{y|x}, \rho_x)$, compute HTE LOD according to (5). Then compute RE for each $(m, n(m))$ compared with the LOD at the $(\rho_{y|x}, \rho_x)$
3. For each $(m, n(m))$, identify the $(\rho_{y|x}, \rho_x)$ with the smallest RE
4. Among the smallest REs, choose the $(m, n(m))$ with the largest RE

KG2: Application to K-DPP

- $m \in [8, 40]$
- $n \in [66, 143]$
- $\rho_{y|x} \in [0.005, 0.1]$
- $\rho_x \in [0.1, 0.75]$

MMD: $m_{opt} = 40, n_{opt} = 66$
96.4% power to detect Δ_{HTE}



KG3: Compound Objective

KG3: Is there a way to adequately power a CRT for both HTE and average treatment effect (ATE) analyses?

- Optimal designs for assessing HTE (minimizing σ^2_{HTE}) may not be optimal for assessing ATE (minimizing σ^2_{ATE})

- Need compound criterion to optimize over that takes both HTE and ATE objectives into account

Weighted combo of single objective REs

LOD under ATE

$$\Theta(\zeta|\lambda) = \lambda \frac{\Theta_{\text{ATE}}(\zeta^*_{\text{ATE}})}{\Theta_{\text{ATE}}(\zeta)} + (1-\lambda)\frac{\Theta_{\text{HTE}}(\zeta^*_{\text{HTE}})}{\Theta_{\text{HTE}}(\zeta)} \quad (6)$$

Priority weight

HTE variance under design ζ

KG3: Compound Maximin

- When there is uncertainty around ICC values:

Compound MMD for assessing HTE and ATE in CRTs

1. Choose priority weight λ
2. Define the parameter space $(\rho_{y|x}, \rho_x)$and design space $(m, n(m))$
3. For each $(\rho_{y|x}, \rho_x)$, compute the LOD for each objective. Then compute $\Theta(\zeta|\lambda)$ for each $(m, n(m))$ compared with their LODs at the $(\rho_{y|x}, \rho_x)$
4. For each $(m, n(m))$, identify the $(\rho_{y|x}, \rho_x)$ with the smallest criterion value
5. Among the smallest criterion values, choose the $(m, n(m))$ with the largest criterion value

KG3: Application to K-DPP

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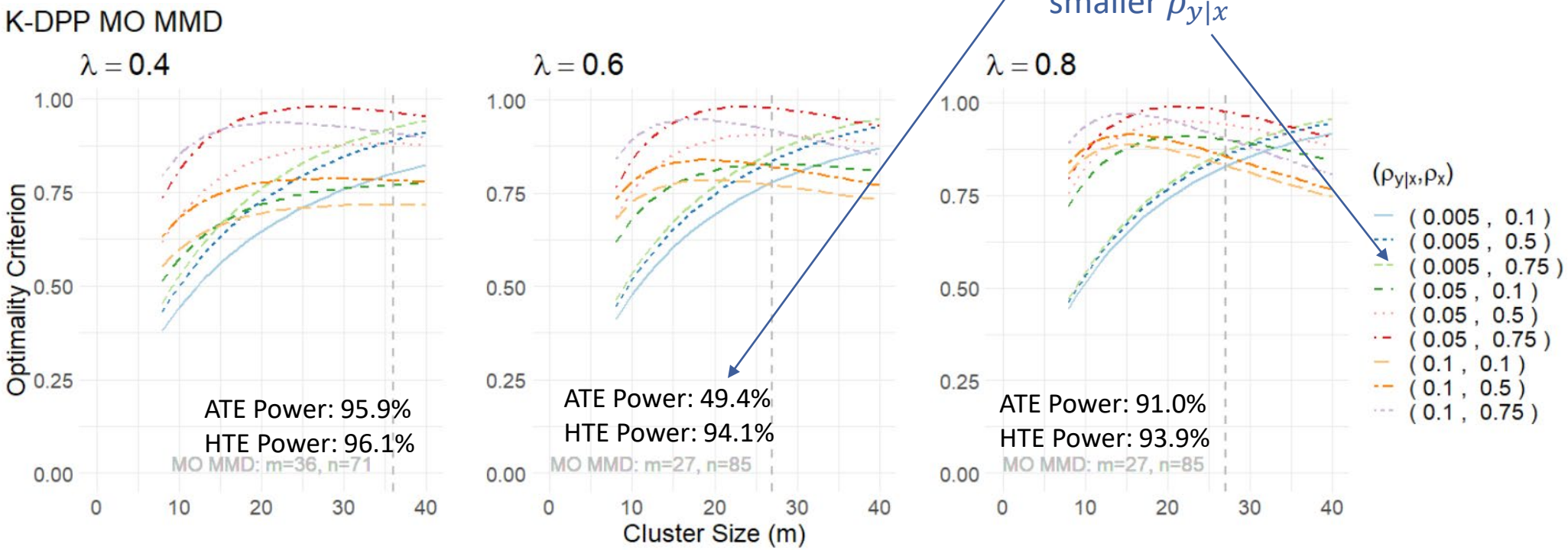
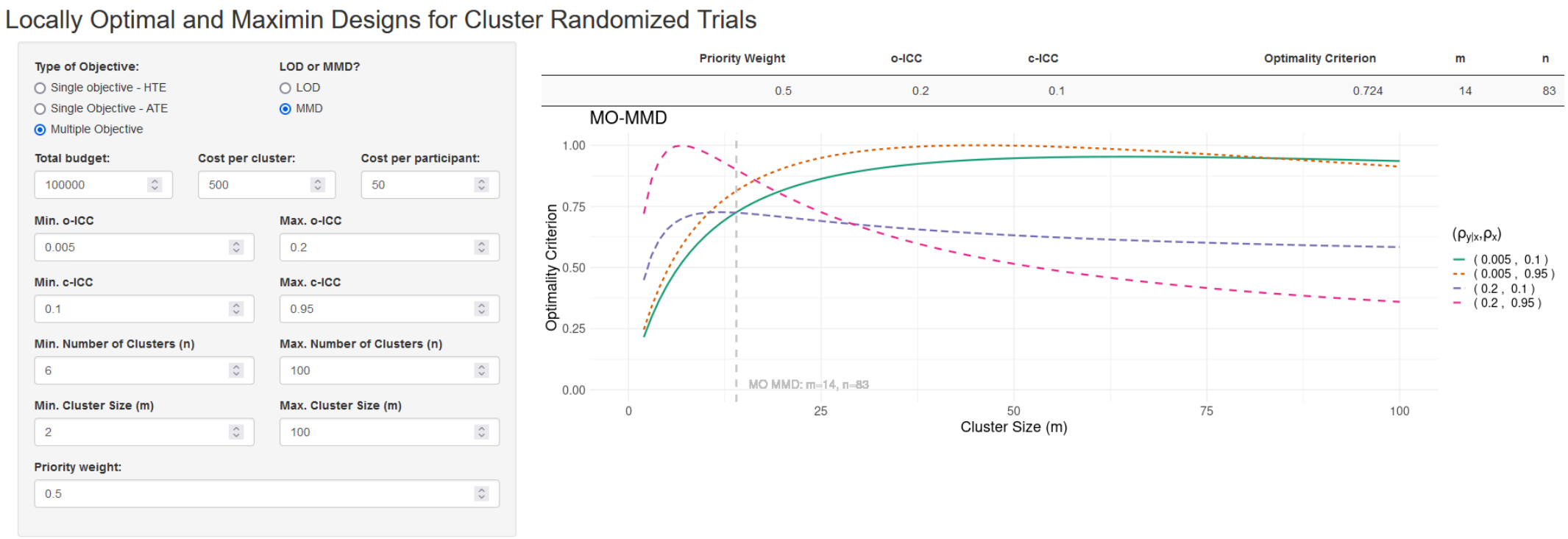


Online Application



Shiny App: https://mary-ryan.shinyapps.io/HTE-MMD-app/

Conclusions

- Understanding treatment effect heterogeneity crucial for improving how and to whom future interventions can be designed and delivered
- Optimal designs free of effect size within budget constraint
- Possible to find maximin designs robust to ICC value misspecification that jointly consider both HTE and ATE objectives

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Thank you!

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Questions?

KG3.1: Compound LOD

- When ICCs are known, find compound LOD by solving for *m* that maximizes $\Theta(\zeta|\lambda)$

$$\max_m \Theta(\zeta|\lambda) = \lambda \frac{\Theta_{\text{ATE}}(\zeta^*_{\text{ATE}})}{\Theta_{\text{ATE}}(\zeta)} + (1-\lambda)\frac{\Theta_{\text{HTE}}(\zeta^*_{\text{HTE}})}{\Theta_{\text{HTE}}(\zeta)}$$
$$= \frac{w_{\text{ATE}}}{\sigma^2_{\text{ATE}}} + \frac{w_{\text{HTE}}}{\sigma^2_{\text{HTE}}}$$

Appendix: Compound LOD

Proposition 2 - Locally optimal compound design

i. If $w_{\mathrm{ATE}} > w_{\mathrm{HTE}}\{(k+1)\rho_{y|x} - \rho_x(k\rho_{y|x}+1)\}$ and $m_{\mathrm{opt}} \leq \frac{B/n-c}{s}$

(A1)

$$m_{\mathrm{opt}} = \frac{-w_{\mathrm{HTE}}k\boxed{a_2} - \sqrt{w_{\mathrm{HTE}}^2k^2\boxed{a_2^2} - 4\{w_{\mathrm{HTE}}(k\boxed{a_1} - \boxed{b_1}) - w_{\mathrm{ATE}}\rho_{y|x}\}\{w_{\mathrm{ATE}}k(1-\rho_{y|x}) + w_{\mathrm{HTE}}k\boxed{a_3}\}}}{2\{w_{\mathrm{HTE}}(k\boxed{a_1} - \boxed{b_1}) - w_{\mathrm{ATE}}\rho_{y|x}\}}$$

$$n_{\mathrm{opt}} = \frac{B}{c + sm_{\mathrm{opt}}}$$

Constants involving ρ_x and $\rho_{y|x}$

ii. Otherwise

$$m_{opt} = \frac{B/n - c}{s}$$

$$n_{\mathrm{opt}} = \frac{B}{c + sm_{\mathrm{opt}}}$$

Appendix: Compound LOD

- Extraneous terms in (A1):

$$a_1 = \rho_{y|x}^2(1-\rho_x)$$
$$a_2 = 2\rho_{y|x}(1-\rho_{y|x})(1-\rho_x)$$
$$a_3 = (1-2\rho_{y|x}+\rho_x\rho_{y|x})(1-\rho_{y|x})$$
$$b_1 = \rho_{y|x}(\rho_x-\rho_{y|x})$$