Society for Clinical Trials

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

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

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

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

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:

per-cluster cost

per-subject cost

$$B = cn + smn = n(c + sm) \Rightarrow n = \frac{B}{c + sm} \quad (3)$$

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

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

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

Only depends on cost ratio (c/s)

ii. Otherwise

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

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

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

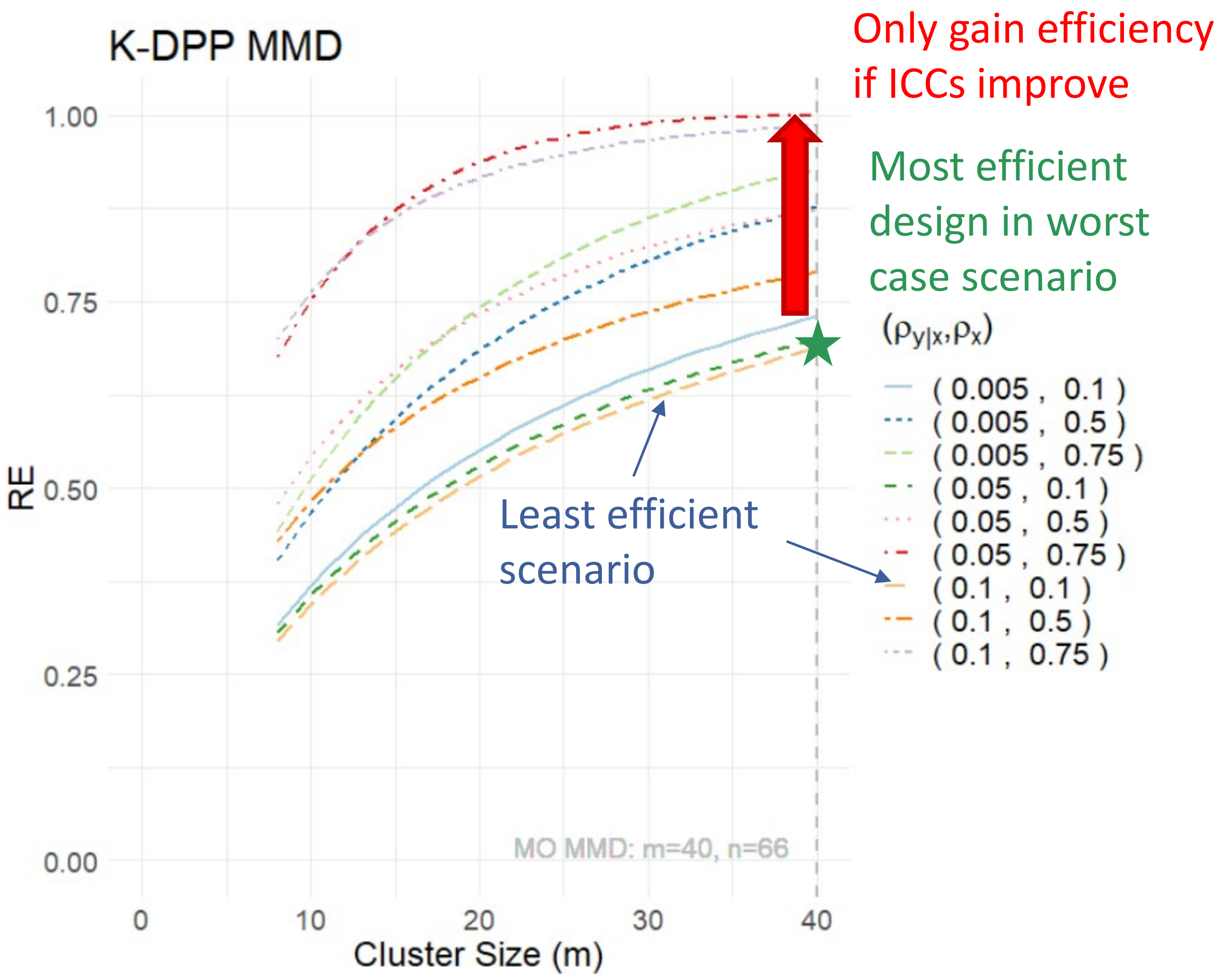
MMD for assessing HTE in CRTs

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}



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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

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

Priority weight

HTE variance under design ζ

KG3: Compound Maximin

- When there is uncertainty around ICC values:

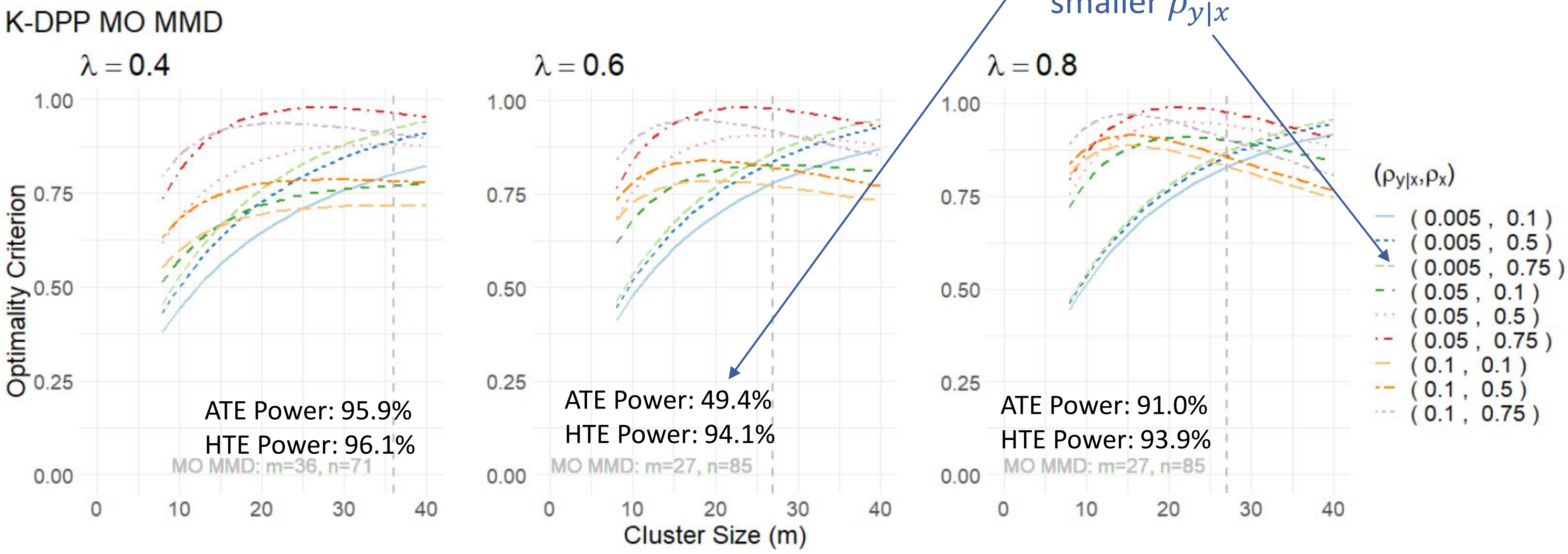
Compound MMD for assessing HTE and ATE in CRTs

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

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

Lower ATE power because MMD under smaller $\rho_{y|x}$



Online Application

Locally Optimal and Maximin Designs for Cluster Randomized Trials

Type of Objective:
- ○ Single objective - HTE
- ○ Single Objective - ATE
- ◉ Multiple Objective

LOD or MMD?
- ○ LOD
- ◉ MMD

Total budget: 100000
Cost per cluster: 500
Cost per participant: 50

Min. o-ICC 0.005
Max. o-ICC 0.2

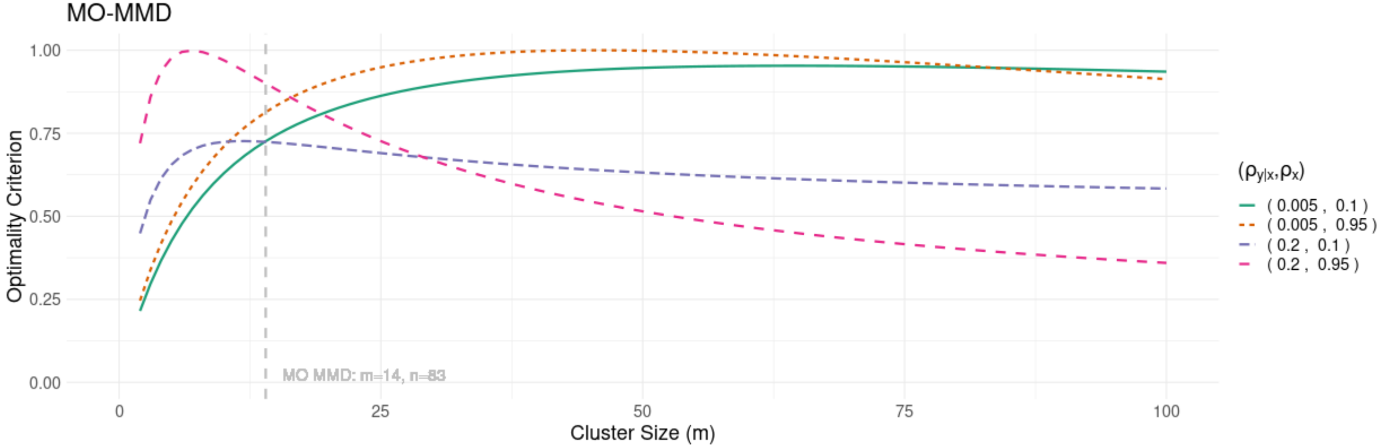
Min. c-ICC 0.1
Max. c-ICC 0.95

Min. Number of Clusters (n) 6
Max. Number of Clusters (n) 100

Min. Cluster Size (m) 2
Max. Cluster Size (m) 100

Priority weight: 0.5

Priority Weight	o-ICC	c-ICC	Optimality Criterion	m	n
0.5	0.2	0.1	0.724	14	83



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

References

Yang, S., Li, F., Starks, M.A., Hernandez, A.F., Mentz, R.J., Choudhury, K.R. (2020). Sample size requirements for detecting treatment effect heterogeneity in cluster randomized trials. *Statistics in Medicine* 39(28): 4218–4237. doi:10.1002/sim.8721

Thankappan KR, Sathish T, Tapp RJ, et al (2018). A peer-support lifestyle intervention for preventing type 2 diabetes in India: A cluster-randomized controlled trial of the Kerala Diabetes Prevention Program. *PLOS Medicine* 15(6): e1002575. doi:10.1371/journal.pmed.1002575

Van Breukelen, G.J. and Candel, M.J. (2015). Efficient design of cluster randomized and multicentre trials with unknown intraclass correlation. *Statistical Methods in Medical Research* 24(5): 540–556. doi:10.1177/0962280211421344

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

(A1) $$m_{\mathrm{opt}} = \frac{-w_{\mathrm{HTE}}ka_2 - \sqrt{w_{\mathrm{HTE}}^2k^2a_2^2 - 4\{w_{\mathrm{HTE}}(ka_1 - b_1) - w_{\mathrm{ATE}}\rho_{y|x}\}\{w_{\mathrm{ATE}}k(1-\rho_{y|x}) + w_{\mathrm{HTE}}ka_3\}}}{2\{w_{\mathrm{HTE}}(ka_1 - b_1) - w_{\mathrm{ATE}}\rho_{y|x}\}}$$

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

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

ii. Otherwise

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

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

Appendix: Compound LOD

- Extraneous terms in (A1):

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

$$a_2 = 2\rho_{y|x}(1 - \rho_{y|x})(1 - \rho_x)$$

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

$$b_1 = \rho_{y|x}\left(\rho_x - \rho_{y|x}\right)$$