Estimating Treatment Effects in Partially Clustered Randomized Controlled Trials with Missing Data: Challenges and Solutions

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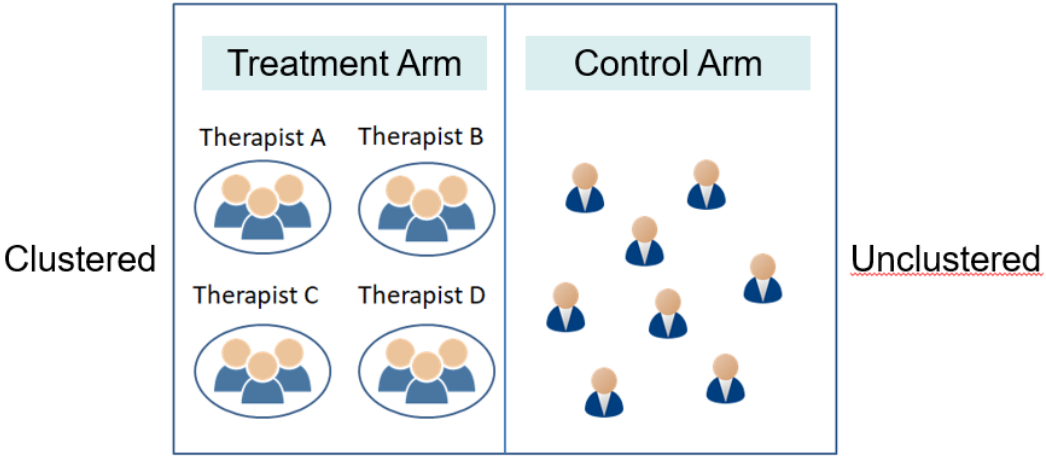
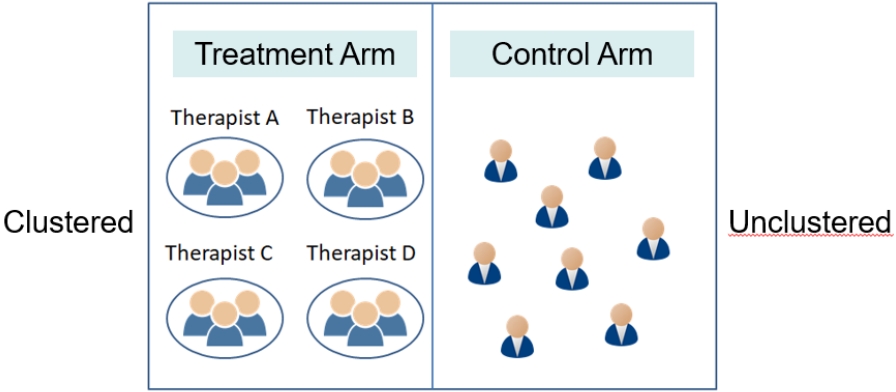
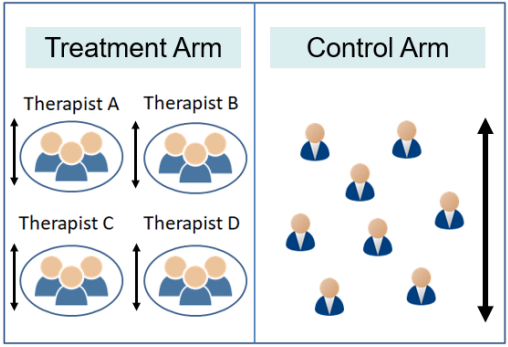

Clustered
Treatment Arm
Control Arm
Therapist A
Therapist B
Therapist C
Therapist D
Unclustered

- **Feature 1: Partially Clustered Structure**

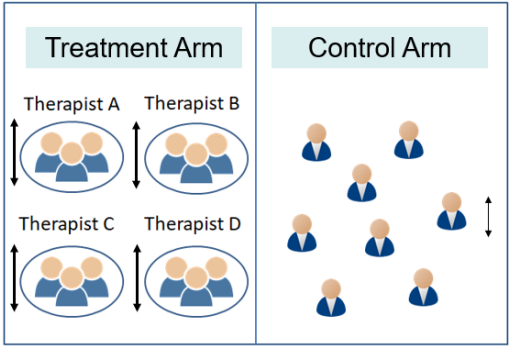


- Feature 1: Partially Clustered Structure
- **Feature 2: Heteroscedastic Residual Variances**

Treatment Variance < Control Variance

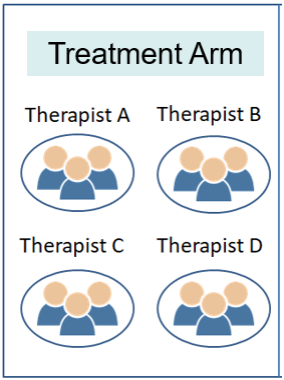


Treatment Variance > Control Variance



Three Key Features of Partially Clustered RCTs

- Feature 1: Partially Clustered Structure
- Feature 2: Heteroscedastic Residual Variances
- **Feature 3: Small Sample Sizes**
  - fewer than 20 clusters, fewer than 30 persons per cluster



- Methods exist to analyze partially clustered data
  - Baldwin et al., 2011; Bauer et al., 2008; Candlish et al., 2018; Kelcey et al., 2020; Lai and Kwok, 2014; Lee and Thompson, 2005; Lohr et al., 2014; Moerbeek and Wong, 2008; Roberts and Roberts, 2005; Lachowicz et al., 2015; Sterba, 2017; Sterba et al., 2014

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- Missing data are inevitable in partially clustered RCTs
- However... little is known on how to handle missing data in partially clustered RCTs

- Three missing data mechanisms (Rubin, 1976)
  - Missing Completely At Random (MCAR)
  - Missing At Random (MAR)
  - Missing Not At Random (MNAR)
- Current study focuses on: **auxiliary-variable-dependent MAR (A-MAR)**
  - auxiliary variable (AV): not of primary research interest but drives missingness
- Both **outcome** and **covariates** could be incomplete
  - person-level covariates (e.g., age, pretest score)
  - cluster-level covariates (e.g., intervention fidelity)

- Issue 1: How to handle **missing covariates** involving random slopes?
  - maximum likelihood estimation (MLE) may not work
  - standard multiple imputation (joint modeling or chained equations) may not work
  - Recommended: **substantive-model-compatible sequential modeling imputation**
    - **sequential modeling multiple imputation (MI-SM)** (Carpenter and Kenward, 2013; Goldstein et al., 2014; Bartlett et al., 2015; Enders et al., 2020; Lüdtke et al., 2020)
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- Issue 2: How to handle **heteroscedastic residual variances**?
  - Recommended: **arm-specific imputation**
    - separate imputations for treatment and control arms (Carpenter and Kenward, 2013; Enders and Gottschall, 2011; Yamaguchi et al., 2020)

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- Issue 3: Do standard missing data handling methods work with **small sample sizes**?

1. **MI-JM-SIM**: simultaneous MI via joint modeling
2. **MI-JM-AS**: arm-specific MI via joint modeling
3. **MI-SM-AS**: arm-specific MI via sequential modeling
4. **SFB-NON**: sequential fully Bayesian estimation using non-informative priors
5. **SFB-WEAK**: sequential fully Bayesian estimation using weakly-informative priors

- In each Bayesian iteration step:
  - Joint modeling (JM): impute **outcome and covariates together**
    - assuming multivariate normality
  - Sequential modeling (SM): impute **covariates first** then impute outcome
    - imputation model compatible with analysis model

- Level-1 (Within Cluster) Model:
  - ANCOVA model with heteroscedastic residual variances

$$Y_{ij} = \beta_{0j} + \beta_{1j} TREAT_{ij} + \beta_{2j} X1_{ij} + e_{ij} \quad (1)$$
$$e_{ij} | (TREAT = 0) \sim N(0, \sigma^2_{e_0}) \quad (2)$$
$$e_{ij} | (TREAT = 1) \sim N(0, \sigma^2_{e_1}) \quad (3)$$

- Level-2 (Between Cluster) Model:
  - fixed intercept (β_{0j}) indicates unclustered control arm
  - random slope of *TREAT* (β_{1j}) indicates clustered treatment arm
  - effect of $X1$ on Y (β_{2j}) could be fixed or random

$$\beta_{0j} = \gamma_{00} \quad (4)$$
$$\beta_{1j} = \gamma_{10} + \gamma_{11} X2_j + u_{1j} \quad (5)$$
$$\beta_{2j} = \gamma_{20} + u_{2j} \quad or \quad \beta_{2j} = \gamma_{20} \quad (6)$$

- **Primary interest: average treatment effect** γ_{10}

Missing Data Model in This Study

- Two auxiliary variables: person-level A1 and cluster-level A2
- Missingness in person-level covariate $X1$ depends on A1
- Missingness in cluster-level covariate $X2$ depends on A2
- Missingness in outcome Y depends on A1 + A2

- Factors manipulated:
  - average treatment effect: 0 or 0.8
  - missing data scenario: incomplete Y and $X1$ vs. incomplete Y and $X2$
  - **No. of clusters:** c **= 4, 8, 16**
  - **cluster size:** m **= 5, 15, 30**
  - ratio of person-level residual variances between arms: $\theta = 0.3, 1, 3$
  - % missing: 10% or 30%
  - $X1$ effect: fixed or random
- $1,000$ Replications
- Compared 5 missing data analysis methods:
  - MI-JM-SIM, MI-JM-AS, MI-SM-AS
  - SFB-NON, SFB-WEAK

Incomplete Variables	Method	% Relative Bias		
		$\theta = 0.3$	$\theta = 1$	$\theta = 3$
Y and X1	MI-JM-SIM	-6.8	-1.5	7.8
	MI-JM-AS	-0.5	-0.8	-0.7
	MI-SM-AS	0.2	-0.1	-0.1
	SFB-NON	-5.1	0.6	**11.2**
	SFB-WEAK	-5.9	-0.2	**10.6**
Y and X2	MI-JM-SIM	-9.6	-4.5	4.7
	MI-JM-AS	-2.7	-1.8	-1.7
	MI-SM-AS	-3.5	-2.4	-2.4
	SFB-NON	-7.7	-0.7	9.6
	SFB-WEAK	-8.5	-1.7	8.7

- $\theta =$ ratio of person-level residual variances between arms

Results: Estimating Cluster-Level Residual Variance

ATE $= 0.8$, **30% missing**

Incomplete Variables	Method	% Relative Bias					
		Fixed X1, $c = 4$			Fixed X1, $c = 8$		
		m=5	15	30	m=5	15	30
Y and X1	MI-JM-SIM	**24.8**	8.4	6.4	**14.3**	1	-0.8
	MI-JM-AS	**24.7**	8.9	6.9	**14.9**	1.8	-0.4
	MI-SM-AS	**204.8**	**27.6**	**12.8**	**74.8**	9.9	1.7
	SFB-NON	**545.4**	**477.8**	**461.8**	**216.9**	**166.8**	**154.5**
	SFB-WEAK	**161.1**	**146.6**	**153.1**	**31**	**29**	**31.3**
Y and X2	MI-JM-SIM	**17.4**	2.8	5.3	8	0.2	0.9
	MI-JM-AS	**24.3**	7.5	9	**11.6**	5.1	5.2
	MI-SM-AS	**185**	**28.6**	**18.9**	**123.6**	**20.5**	**12.8**
	SFB-NON	**536.1**	**473.2**	**460.3**	**212.4**	**168.4**	**159.1**
	SFB-WEAK	**132.4**	**109.6**	**116.6**	**19.6**	**20.8**	**25.3**

- $c =$ No. of clusters
- $m =$ cluster size

Results: Estimating Cluster-Level Residual Variance (Cont.)

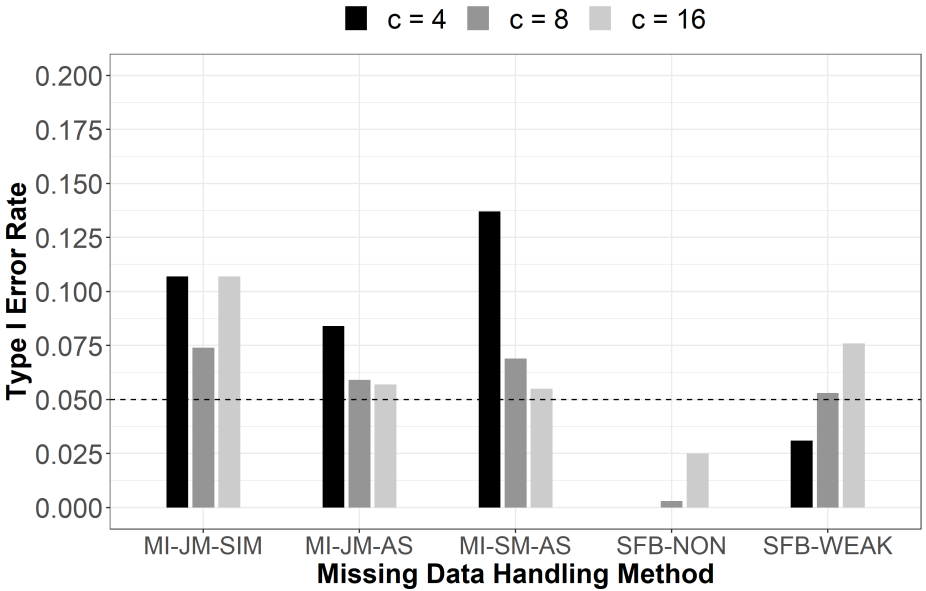
ATE $= 0.8$, **30% missing**

Incomplete Variables	Method	% Relative Bias					
		Fixed X1, $c = 16$			Random X1, $c = 16$		
		m=5	15	30	m=5	15	30
Y and X1	MI-JM-SIM	8.5	1.7	0.6	**-58.1**	**-70.7**	**-70.5**
	MI-JM-AS	8	2.6	1	**-51.9**	**-68.9**	**-69.6**
	MI-SM-AS	**21.3**	6.3	1.8	**39.8**	7.4	-0.3
	SFB-NON	**106.2**	**75.7**	**67.4**	**170.9**	**91.1**	**70.4**
	SFB-WEAK	3.5	**10**	**10.8**	**37.2**	8.9	7.9
Y and X2	MI-JM-SIM	0.8	-1.3	0.1	**-46.4**	**-56.8**	**-56.9**
	MI-JM-AS	4.5	2.9	4.1	**-43**	**-56**	**-56.4**
	MI-SM-AS	**22.4**	9.4	7.9	**32.8**	3.8	-3
	SFB-NON	**102.4**	**75.4**	**69.2**	**169.3**	**95**	**76.3**
	SFB-WEAK	-5.4	4.3	7.6	**38.5**	**17.7**	**16.1**

- $c =$ No. of clusters
- $m =$ cluster size

Results: Type I Error for Detecting Treatment Effect

fixed $X1$ effect, 30% missing, $m = 30$, $\theta = 0.3$



- Which methods perform the best in handling A-MAR data in partially clustered RCT?

Arm-specific MI methods

If $X1$ effect is...	Best Performing Method
Fixed	MI-JM-AS (joint modeling)
Random	MI-SM-AS (sequential modeling)

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- MI of the entire sample assuming equal residual variance across arms (MI-JM-SIM) is not recommended.

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- MI of the entire sample assuming equal residual variance across arms (MI-JM-SIM) is not recommended.
- Sequential fully Bayesian approach is not recommended.

References

- Baldwin, S. A., Bauer, D. J., Stice, E., & Rohde, P. (2011). Evaluating models for partially clustered designs. *Psychological Methods*, 16 (2), 149-165.
- Bauer, D. J., Sterba, S. K., & Hallfors, D. D. (2008). Evaluating group-based interventions when control participants are ungrouped. *Multivariate Behavioral Research*, 43 (2), 210-236.
- Candlish, J., Teare, M., Dimairo, M., Flight, L., Mandefield, L., & Walters, S. (2018). Appropriate statistical methods for analysing partially nested randomised controlled trials with continuous outcomes: A simulation study. *BMC Medical Research Methodology*, 18 (1), 1-17.
- Kelcey, B., Bai, F., & Xie, Y. (2020). Statistical power in partially nested designs probing multilevel mediation. *Psychotherapy Research*, 30 (8), 1061-1074.
- Lee, K. J., & Thompson, S. G. (2005). The use of random effects models to allow for clustering in individually randomized trials. *Clinical Trials*, 2 (2), 163-173.
- Lohr, S. L., Schochet, P. Z., & Sanders, E. A. (2014). Partially nested randomized controlled trials in education research: A guide to design and analysis (tech. rep.). National Center for Education Research, Institute of Education Sciences, U.S. Department of Education.
- Roberts, C., & Roberts, S. A. (2005). Design and analysis of clinical trials with clustering effects due to treatment. *Clinical Trials*, 2 (2), 152-162.
- Lachowicz, M. J., Sterba, S. K., & Preacher, K. J. (2015). Investigating multilevel mediation with fully or partially nested data. *Group Processes and Intergroup Relations*, 18 (3), 274-289.
- Sterba, S. K., Preacher, K. J., Forehand, R., Hardcastle, E. J., Cole, D. A., & Compas, B. E. (2014). Structural equation modeling approaches for analyzing partially nested data. *Multivariate Behavioral Research*, 49 (2), 93-118.

References

- Rubin, D. B. (1976). Inference and missing data. *Biometrika*, 63 (3), 581-592.
- Carpenter, J. R., & Kenward, M. G. (2013). *Multiple imputation and its application*. Chichester, West Sussex, United Kingdom: John Wiley & Sons.
- Goldstein, H., Carpenter, J. R., & Browne, W. J. (2014). Fitting multilevel multivariate models with missing data in responses and covariates that may include interactions and non-linear terms. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, 177 (2), 553-564.
- Bartlett, J. W., Seaman, S. R., White, I. R., & Carpenter, J. R. (2015). Multiple imputation of covariates by fully conditional specification: Accommodating the substantive model. *Statistical Methods in Medical Research*, 24 (4), 462-487.
- Enders, C. K., Du, H., & Keller, B. T. (2020). A model-based imputation procedure for multilevel regression models with random coefficients, interaction effects, and nonlinear terms. *Psychological Methods*, 25 (1), 88-112.
- Lüdtke, O., Robitzsch, A., & West, S. G. (2020). Regression models involving nonlinear effects with missing data: A sequential modeling approach using Bayesian estimation. *Psychological Methods*, 25 (2), 157-181.
- Erler, N. S., Rizopoulos, D., Rosmalen, J. v., Jaddoe, V. W., Franco, O. H., & Lesaffre, E. M. (2016). Dealing with missing covariates in epidemiologic studies: a comparison between multiple imputation and a full Bayesian approach. *Statistics in Medicine*, 35 (17), 2955-2974.
- Zhang, Q., & Wang, L. (2017). Moderation analysis with missing data in the predictors. *Psychological Methods*, 22 (4), 649-666.
- Enders, C. K., & Gottschall, A. C. (2011). Multiple imputation strategies for multiple group structural equation models. *Structural Equation Modeling*, 18 (1), 35-54.
- Yamaguchi, Y., Ueno, M., Maruo, K., & Gosho, M. (2020). Multiple imputation for longitudinal data in the presence of heteroscedasticity between treatment groups. *Journal of Biopharmaceutical Statistics*, 30 (1), 178-196.

Thank you !

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