Methods: Mind the Gap
Webinar Series

Analysis of Multiple-Period Group-Randomized Trials: Random Coefficients Model or Repeated Measures ANOVA?

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Overview

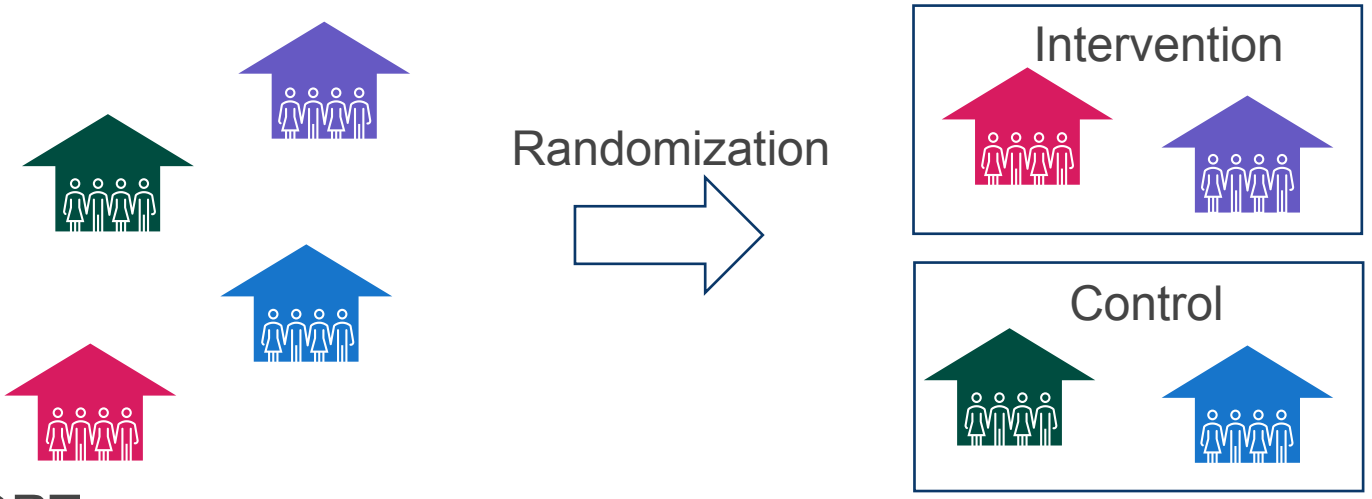
- Based on Moyer et al. (2022).
- Outline:
  - Background
  - Method
    - Aims
    - Data Generating Mechanisms
    - Target and Performance Metric
    - Analytic Models
  - Results
  - Discussion
  - Questions

- Disclaimer: The views expressed in this presentation are those of the speaker and do not necessarily reflect the position or policy of the NIH or the U.S. government.

Moyer JC, et al. Analysis of multiple-period group randomized trials: Random coefficients model or repeated measures ANOVA? Trials. 2022 Dec 7;23(1):987.

Background

- Group-randomized trials (GRTs) randomly assign groups to treatment conditions.



- Challenges with GRTs:
  - Outcome measures within groups are likely to be correlated, may inflate Type I error rate if ignored.
  - A small number of groups or clusters (<40) provides limited degrees of freedom for hypothesis tests.
  - GRTs tends to be more complicated to design, analyze, and report, and are prone to bias.
- When might a GRT be necessary?
  - Intervention operates at the group level.
  - Manipulation of physical or social environment.
  - Intervention cannot be delivered to individuals due to the potential for contamination.

Background

- Multiple period GRTs spanning two or more time periods allow for several design configurations.
- **Parallel GRT:** Separate but parallel intervention and control conditions throughout the trial, with no crossover.

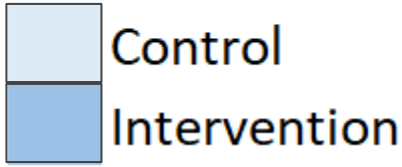
Group	Period 1	Period 2	Period 3	Period 4
1				
2				
3				
4				
5				
6				

Control
Intervention

Background

- **Crossover GRT:** Groups randomly assigned to intervention but switch status at least once over the course of the trial.

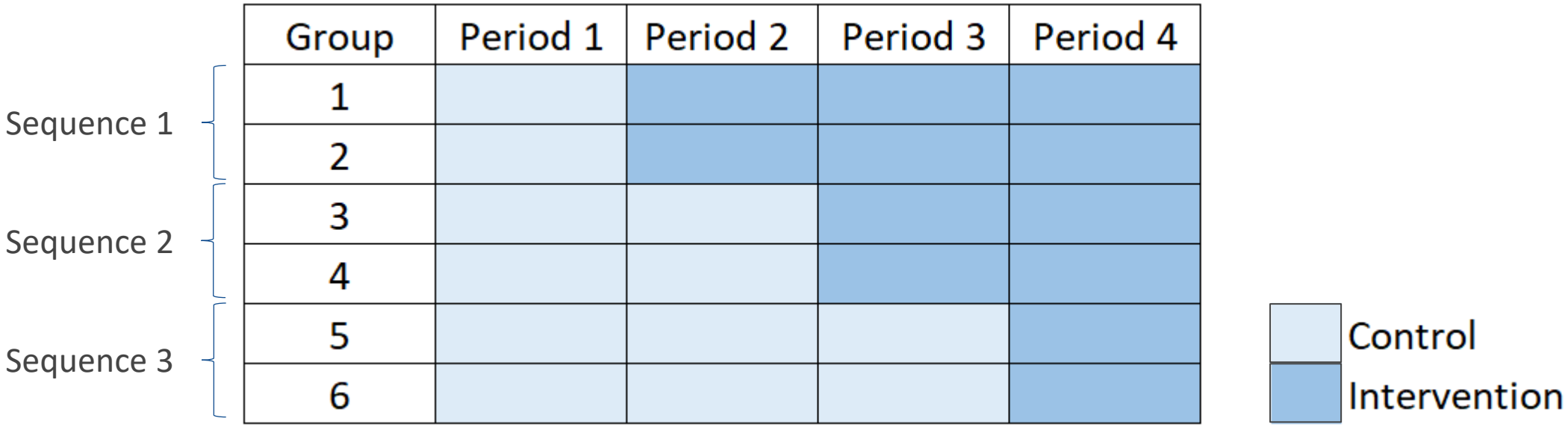
Group	Period 1	Period 2	Period 3	Period 4
1				
2				
3				
4				
5				
6				



- Statistically efficient.
- Only appropriate for interventions on chronic or stable conditions.
- Carry-over effects might require lengthy wash-out periods.

Background

- **Stepped Wedge GRT:** Groups randomized to sequences, crossover to intervention sequentially in staggered steps until all groups receive the intervention.



- Especially complicated to design, implement, analyze, and report.
- Use of SWGRTs should have strong justification.

Hemming K, Taljaard M. Reflection on modern methods: When is a stepped-wedge cluster randomized trial a good study design choice? Int J Epidemiol. 2020;49(3):1043-1052. Epub 2020/05/09. PMID: 32386407.

Background

- **Parallel GRT:** Separate but parallel intervention and control conditions throughout the trial, with no crossover.

Group	Period 1	Period 2	Period 3	Period 4
1				
2				
3				
4				
5				
6				

Control
Intervention

Background

- GRT designs for two or more time periods can be classified according to the presence of repeat observations.
- **Cross-Sectional**: different individuals are observed at each period.
  - Minnesota Heart Health Program
    - 6 communities with 300-500 individuals per community were surveyed at regular time periods on various health outcomes.
- **Closed Cohort**: the same individuals are observed at each period.
  - Teens Eating and Nutrition Study
    - 16 schools with 52-344 students/school followed over time to assess an intervention to improve nutrition among 7th and 8th graders.

Luepker RV, et al. Community education for cardiovascular disease prevention: Risk factor changes in the Minnesota Heart Health Program. Am J Public Health. 1994;84(9):1383–93.
Lytle LA, et al. School-based approaches to affect adolescents' diets: results from the TEENS study. Health Educ Behav. 2004;31(2):270–87.

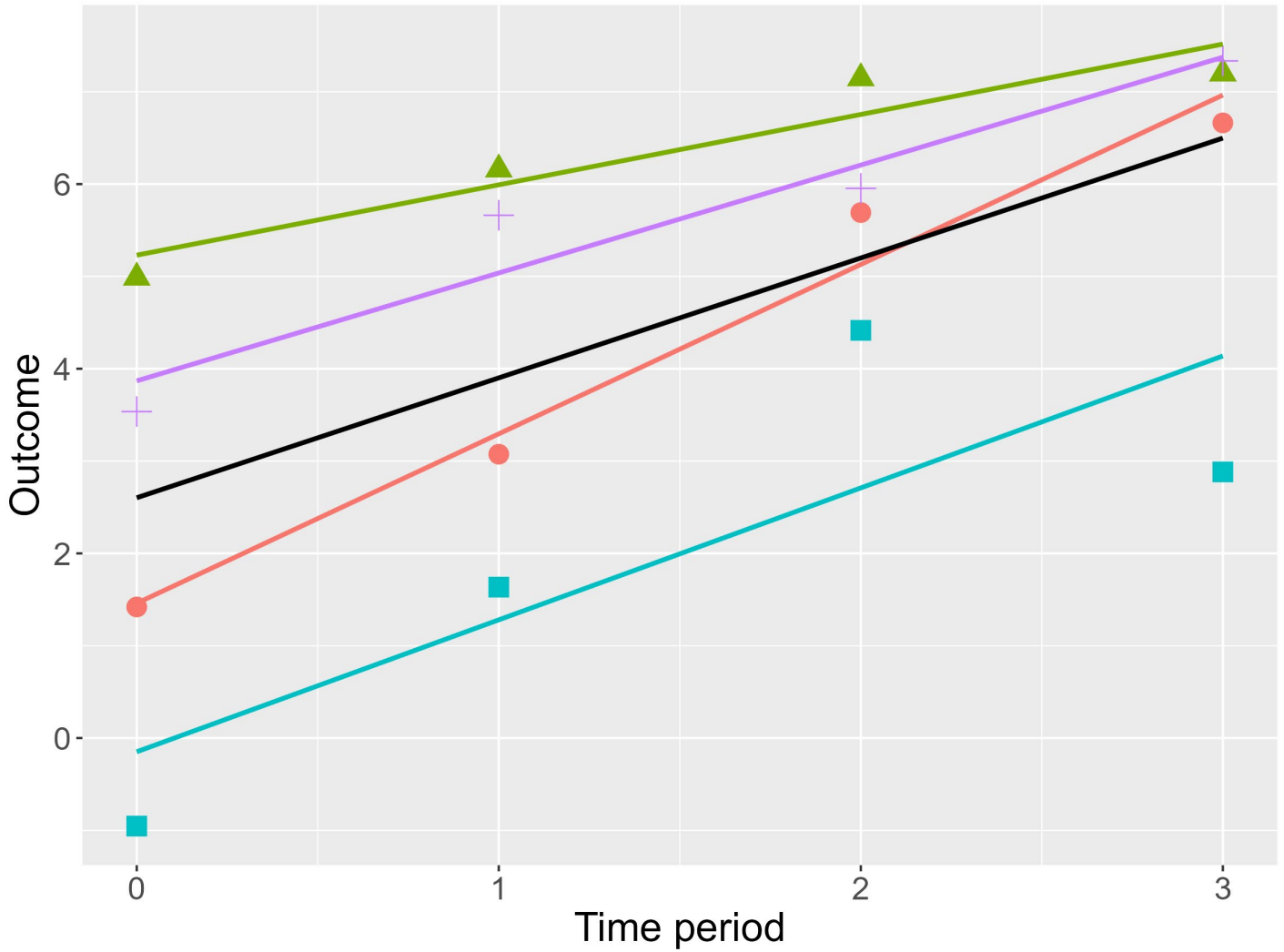
Background

- Analytic models for multiple-period GRTs require several decisions about how best to specify the primary analysis.
  - Both individuals and groups may be followed longitudinally, each require an appropriate longitudinal correlation model.
- Key considerations:
  - Representing time in the mean model as categorical or continuous.
  - Specification of random effects to generate:
    - Longitudinal correlations within an individual
    - Correlation among individuals from the same group
  - Choice of a covariance matrix for any random effects.

Background

- A key consideration for multiple-period parallel GRTs is representing time as categorical or continuous.
- **Random Coefficients (RC)**: Represent time as continuous in group-specific mean models.
  - Random effects used to induce correlation among repeated observations sharing the same group- or member-specific trajectory.
  - Random effects represent group- or member-level deviations from arm-specific intercepts and slopes.
  - Potentially use polynomial terms.

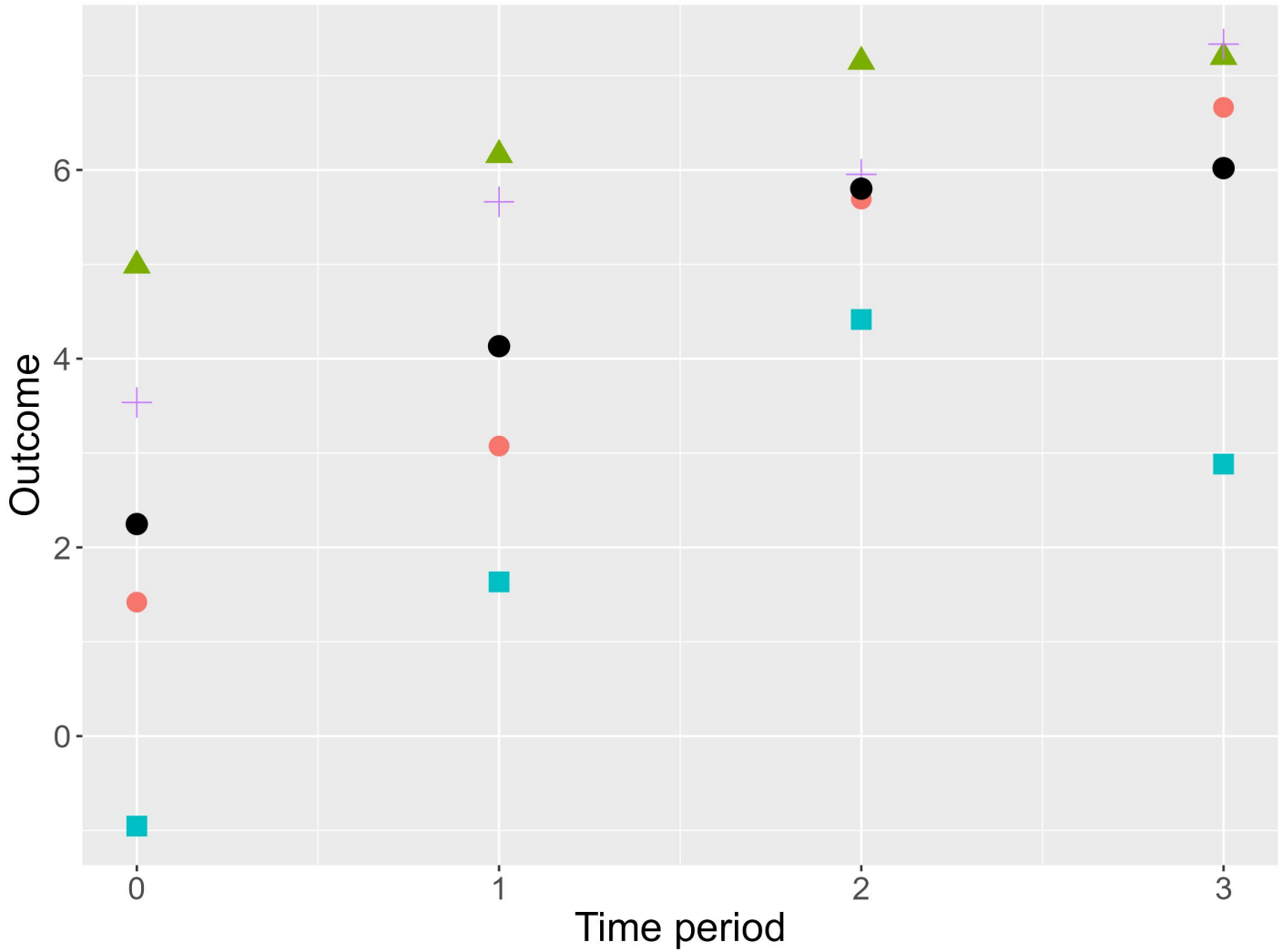
Background – Random Coefficients



Background

- **Repeated Measures ANOVA (RM-ANOVA)**: Represent time as categorical using time-specific indicators.
  - Random effects represent group- or member-level deviations from time-specific arm means.
  - Multiple approaches to modeling covariance:
    - Simple random intercept model having only time-invariant random effects.
    - Exchangeable model allowing for both time-invariant and time-varying random effects.
    - Unstructured covariance for repeated measures on an individual.
- **Saturated:** Represent time as categorical using time-specific indicators.
  - Models specifying only time-varying random effects at both group- and member-levels.
  - Unstructured covariance.

Background – Repeated Measures ANOVA



Background

- Murray et al. (1998) conducted a simulation study to compare the performance of RC and RM-ANOVA analytic models in cross-sectional parallel GRT data.
  - Particularly interested in preserving type I error rates for the null hypothesis of no differential trends.
    - i.e., the interaction between condition and time.
  - Simulated datasets assuming RC or RM-ANOVA mechanisms.
  - RC analytic models with UN covariance.
  - RM-ANOVA analytic models with variance components (VC) covariance matrix.
- RC analytic models:
  - Maintained nominal type I error rates for RC and RM-ANOVA data.
- RM-ANOVA analytic models:
  - Maintained nominal type I error rates for RM-ANOVA data.
  - Exhibited inflated type I error rates for RC data.
- RC analytic models were recommended for multiple period parallel GRTs.

Murray DM, et al. Analysis of data from group-randomized trials with repeat observations on the same groups. Stat Med. 1998;17(14):1581-600.

Background

- Few publications since then have compared RM-ANOVA and RC approaches in the context of parallel GRTs.
- Kasza and Forbes (2019)
  - Investigated the impact of mis-specifying correlation structures in the RM-ANOVA setting.
  - For example: assuming correlation between outcomes within the same group at different time periods is the same, but it decays as a function of time.
  - Did not investigate RC analytic models, but noted further work was required.
- Bell et al. (2019)
  - Omitting random slopes in analytic models when such variation exists in the data generating mechanism results in standard error estimates that are too small.

Kasza J and Forbes AB. Inference for the treatment effect in multiple-period cluster randomised trials when random effect correlation structure is misspecifed. Stat Methods Med Res. 2019;28(10-11):3112-3122.
Bell A, et al. Fixed and random effects models: making an informed choice. Quality & Quantity. 2019;53:1051–1074.

Background

- Bell and Rabe (2020) applied the mixed model for repeated measures to multiple-period, cohort parallel GRTs.
  - RM-ANOVA model with a random effect for group, no time x group random effect, UN covariance at the member level.
  - Simulated data sets assuming an RM-ANOVA mechanism with and without a time x group component of variation.
  - Their main interest was the intervention effect at the final time period.
- Nominal type I error rate when applying their analytic model to data with no time x group variation.
- Inflated type I error rate when applying their analytic model to data with time x group variation.

Bell ML and Rabe BA. The mixed model for repeated measures for cluster randomized trials: a simulation study investigating bias and type I error with missing continuous data. Trials. 2020;21(1):148.

Method – Aims

- Three key questions:

1. Would Murray et al. (1998) have found better performance with RM-ANOVA analytic models using UN covariance for cross-sectional data?
   - VC covariance makes strong assumptions about the independence of random effects, UN makes no assumptions.
2. Would Murray et al. have seen patterns in cohort data like those they saw with cross-sectional data?
   - Cohort data has a more complex covariance structure.
3. How important is the time x group random effect term in the analytic model if the data generation mechanism also includes variability at that level?
   - Murray et al. did not investigate omitting this term.

Method – Data Generating Mechanisms

- RM-ANOVA Data Generating Mechanism

Cross-sectional:

$$Y_{ijkl} = \mu + C_l + T_j + TC_{jl} + \mathbf{G}_{kl} + \mathbf{TG}_{jkl} + \epsilon_{ijkl} \quad (1)$$

Cohort:

$$Y_{ijkl} = \mu + C_l + T_j + TC_{jl} + \mathbf{G}_{kl} + \mathbf{TG}_{jkl} + \mathbf{M}_{ikl} + \epsilon_{ijkl} \quad (2)$$

Y_{ijkl}	continuous outcome for *i*th member in *k*th group and *l*th condition at *j*th time
μ	mean outcome in the control condition at baseline
C_l	baseline difference between the mean the *l*th condition and control condition mean (C_1=0)
T_j	difference between the mean outcome of the *j*th time period with baseline control condition mean (T_1=0)
TC_{jl}	time x condition interaction for the *l*th condition at the *j*th time period ($TC_{1l} = TC_{j1} = 0$)
$\mathbf{G}_{kl}$	random intercept for the *k*th group in the *l*th condition ("time-invariant")
$\mathbf{TG}_{jkl}$	random intercept for the *k*th group at the *j*th time in the *l*th condition ("time-varying", "time by group")
$\mathbf{M}_{ikl}$	random intercept for the *i*th individual in the *k*th group in the *l*th condition
ϵ_{ijkl}	residual error

Random effects are independent and distributed as $\mathbf{G}_{kl} \sim N(0, \sigma_g^2)$, $\mathbf{TG}_{jkl} \sim N(0, \sigma_{tg}^2)$, $\mathbf{M}_{ikl} \sim N(0, \sigma_m^2)$, and $\epsilon_{ijkl} \sim N(0, \sigma_\epsilon^2)$.

Method – Data Generating Mechanisms

- RC Data Generating Mechanism

Cross-sectional:

$$Y_{ijkl} = \mu + C_l + T_{(\text{lin})} \cdot t_j + T_{(\text{lin})} C_l \cdot t_j + \mathbf{G}_{kl} + \mathbf{T}_{(\text{lin})} \mathbf{G}_{kl} \cdot t_j + \epsilon_{ijkl} \quad (3)$$

Cohort:

$$Y_{ijkl} = \mu + C_l + T_{(\text{lin})} \cdot t_j + T_{(\text{lin})} C_l \cdot t_j + \mathbf{G}_{kl} + \mathbf{T}_{(\text{lin})} \mathbf{G}_{kl} \cdot t_j + \mathbf{M}_{kl} + \mathbf{T}_{(\text{lin})} \mathbf{M}_{kl} \cdot t_j + \epsilon_{ijkl} \quad (4)$$

Terms appearing on this slide and the previous slide are defined similarly.

t_j	time value at the *j*th time period
$T_{(\text{lin})}$	linear effect of time
$T_{(\text{lin})}C$	linear interaction between time and condition
$\mathbf{T}_{(\text{lin})}\mathbf{G}_{kl}$	random slope for the *k*th group in the *l*th condition.
$\mathbf{T}_{(\text{lin})}\mathbf{M}_{ikl}$	random slope for the *i*th individual in the *k*th group in the *l*th condition

All random effects are independent, with $\mathbf{T}_{(\text{lin})}\mathbf{G}_{kl} \sim N(0, \sigma^2_{t(lin)g})$ and $\mathbf{T}_{(\text{lin})}\mathbf{M}_{ikl} \sim N(0, \sigma^2_{t(lin)m})$.

Method – Data Generating Mechanisms

- Intraclass correlation (ICC) measures the fraction of total variation attributable to groups within a period.
- For RM-ANOVA:
  - Cross-Sectional: $$ICC = \frac{\sigma_g^2 + \sigma_{tg}^2}{\sigma_g^2 + \sigma_{tg}^2 + \sigma_\epsilon^2}$$
  - Cohort: $$ICC = \frac{\sigma_g^2 + \sigma_{tg}^2}{\sigma_g^2 + \sigma_{tg}^2 + \sigma_m^2 + \sigma_\epsilon^2}$$
- For RC, for a given set of variances ICC is a nonconstant function with time (Li et al., 2020).
- To simplify presentation of results, RM-ANOVA ICC definition will be used.

Li F, et al. Mixed-effects models for the design and analysis of stepped wedge cluster randomized trials: An overview. Stat Methods Med Res. 2021;30(2):612–639.

Method – Data Generating Mechanisms

- Between period correlations can be expressed as autocorrelations.
- Cluster Autocorrelation (CAC): over-time correlation of the outcome variable at the group level.

$$CAC = \frac{\sigma_g^2}{\sigma_g^2 + \sigma_{tg}^2}$$

- Individual Autocorrelation (IAC): over-time correlation of the outcome variable at the member-level (cohort only).

$$IAC = \frac{\sigma_m^2}{\sigma_m^2 + \sigma_\epsilon^2}$$

Method – Data Generating Mechanisms

- Generated cross-sectional and cohort data for both RM-ANOVA and RC models.
- All simulations:
  - 2 conditions
  - Five equally spaced time periods (0 to 4)
  - 40 members per group
- Groups per condition: 10, 20, 40
- All fixed effect parameters were set to 0.
- Random effects variances chosen to have ICCs of 0.100, 0.010, and 0.001 under RM-ANOVA.
- Random effects variances chosen to have CAC = 0.50 and IAC = 0.70.
- 1000 replications for each data structure (cohort, cross-sectional), groups per condition value (10, 20, 40), and ICC value (0.100, 0.01, 0.001)

Method – Target and Performance Metric

- Our interest was in differential change over time – that is, the time x condition interaction.
- **Target:** The null hypothesis of no fixed effect time x condition interaction.
- This is a different for the various approaches:
  - RM-ANOVA: No difference in the pattern of condition means over time between intervention and control conditions.
  - RC: No difference in linear slope between intervention and control conditions.
- **Performance Metric:** Assess the type I error rates of multiple analytic models.

$$P(\text{Reject } H_0 | H_0 \text{ is true}) = \frac{1}{1000} \sum_{i=1}^{1000} \mathbb{I}(p_i < 0.05)$$

Method – Analytic Models

- General linear mixed model:

For the *i*th individual:

$$\mathbf{Y}_i = \mathbf{X}_i\beta + \mathbf{Z}_i\gamma_i + \epsilon_i$$

- $\mathbf{Y}_i$: vector of observed continuous outcomes
- β: vector of fixed effects (including intercept)
- $\mathbf{X}_i$: design matrix for fixed effects
- γ_i: vector of random effects
- $\mathbf{Z}_i$: design matrix for random effects
- ϵ_i: residual error

- $\gamma_i \sim N(0, \mathbf{G})$ and $\epsilon_i \sim N(0, \mathbf{R})$, with γ_i and ϵ_i independent, where **G** and **R** are random effects and residual error covariance matrices, respectively.
- SAS offers many options for fitting covariance matrices **G** and **R**.

Method – Analytic Models

- **Variance Components, VC**: Independent variance component for each random term.
  - Example: **G** matrix for RM-ANOVA model 1 with five time periods:

$$\begin{bmatrix} \sigma_g^2 & 0 & 0 & 0 & 0 & 0 \\ 0 & \sigma_{tg}^2 & 0 & 0 & 0 & 0 \\ 0 & 0 & \sigma_{tg}^2 & 0 & 0 & 0 \\ 0 & 0 & 0 & \sigma_{tg}^2 & 0 & 0 \\ 0 & 0 & 0 & 0 & \sigma_{tg}^2 & 0 \\ 0 & 0 & 0 & 0 & 0 & \sigma_{tg}^2 \end{bmatrix}$$

Method – Analytic Models

- **Compound Symmetric, CS**: Assume random effects have the same variance at each time period and constant covariance.
  - Example: **R** matrix for the cohort RM-ANOVA (model 2) with five time periods:

$$\begin{bmatrix} \sigma_m^2 + \sigma_e^2 & \sigma_m^2 & \sigma_m^2 & \sigma_m^2 & \sigma_m^2 \\ \sigma_m^2 & \sigma_m^2 + \sigma_e^2 & \sigma_m^2 & \sigma_m^2 & \sigma_m^2 \\ \sigma_m^2 & \sigma_m^2 & \sigma_m^2 + \sigma_e^2 & \sigma_m^2 & \sigma_m^2 \\ \sigma_m^2 & \sigma_m^2 & \sigma_m^2 & \sigma_m^2 + \sigma_e^2 & \sigma_m^2 \\ \sigma_m^2 & \sigma_m^2 & \sigma_m^2 & \sigma_m^2 & \sigma_m^2 + \sigma_e^2 \end{bmatrix}$$

Method – Analytic Models

- **Unstructured, UN**: Separate variances for each random effect/residual, and separate covariances for pairs of random effects/residuals.
  - Example: **R** matrix for the cohort RM-ANOVA (model 2) with five time periods:

$$\begin{bmatrix} \sigma_1^2 & \sigma_{12} & \sigma_{13} & \sigma_{14} & \sigma_{15} \\ \sigma_{12} & \sigma_2^2 & \sigma_{23} & \sigma_{24} & \sigma_{25} \\ \sigma_{13} & \sigma_{23} & \sigma_3^2 & \sigma_{34} & \sigma_{35} \\ \sigma_{14} & \sigma_{24} & \sigma_{34} & \sigma_4^2 & \sigma_{45} \\ \sigma_{15} & \sigma_{25} & \sigma_{35} & \sigma_{45} & \sigma_5^2 \end{bmatrix}$$

Method – Analytic Models

- **Unstructured independent, UN(1)**: Separate variances for each random effect/residual and no covariance.
  - Example: **R** matrix for the cohort RM-ANOVA (model 2) with five time periods:

$$\begin{bmatrix} \sigma_1^2 & 0 & 0 & 0 & 0 \\ 0 & \sigma_2^2 & 0 & 0 & 0 \\ 0 & 0 & \sigma_3^2 & 0 & 0 \\ 0 & 0 & 0 & \sigma_4^2 & 0 \\ 0 & 0 & 0 & 0 & \sigma_5^2 \end{bmatrix}$$

Method – Analytic Models

- Four analytic models were fit to each data set.
  - All models contained fixed effects for time, condition, and their interaction

1. **RM-ANOVA with VC covariance**
   - Random effects: group, time x group

   a) Cross-sectional:
      - **G** matrix: VC

   b) Cohort:
      - **G** matrix: VC
      - **R** matrix: CS

- 1a was the RM-ANOVA approach studied by Murray et al. (1998).
- 1b was used to address Aim 2.
  - *Would Murray et al. have seen patterns in cohort data like those they saw with cross-sectional data?*

Method – Analytic Models

- Four analytic models were fit to each data set.
  - All models contained fixed effects for time, condition, and their interaction

2. RM-ANOVA with UN covariance

- Random effects: group, time x group

a) Cross-sectional:
   - **G** matrix: UN

b) Cohort:
   - **G** matrix: VC
   - **R** matrix: UN

- 2a is used to address Aim 1:
  - *Would Murray et al. (1998) have found better performance with RM-ANOVA analytic models using UN covariance for cross-sectional data?*
- 2b was inspired by Bell and Rabe (2021).

Method – Analytic Models

- Four analytic models were fit to each data set.
  - All models contained fixed effects for time, condition, and their interaction

3. Random Coefficients (RC)

a) Cross-sectional:
- Random effects: group, time x group
- **G** matrix: UN

b) Cohort:
- Random effects: group, time x group, member, time x member
- **G** matrix: UN

- R matrix is not specified as member-level random effects were explicitly modeled.
- 3a is the RC approach studied by Murray et al. (1998).
- 3b is used to address Aim 2:
  - *Would Murray et al. have seen patterns in cohort data like those they saw with cross-sectional data?*

Method – Analytic Models

- Four analytic models were fit to each data set.
  - All models contained fixed effects for time, condition, and their interaction

4. Saturated

- Random effects: time x group

a) Cross-sectional
   - **G** matrix: UN
   - **R** matrix: UN(1)

b) Cohort
   - **G** matrix: UN
   - **R** matrix: UN

- 4a and 4b were not studied by Murray et al. (1998).

Method – Analytic Models

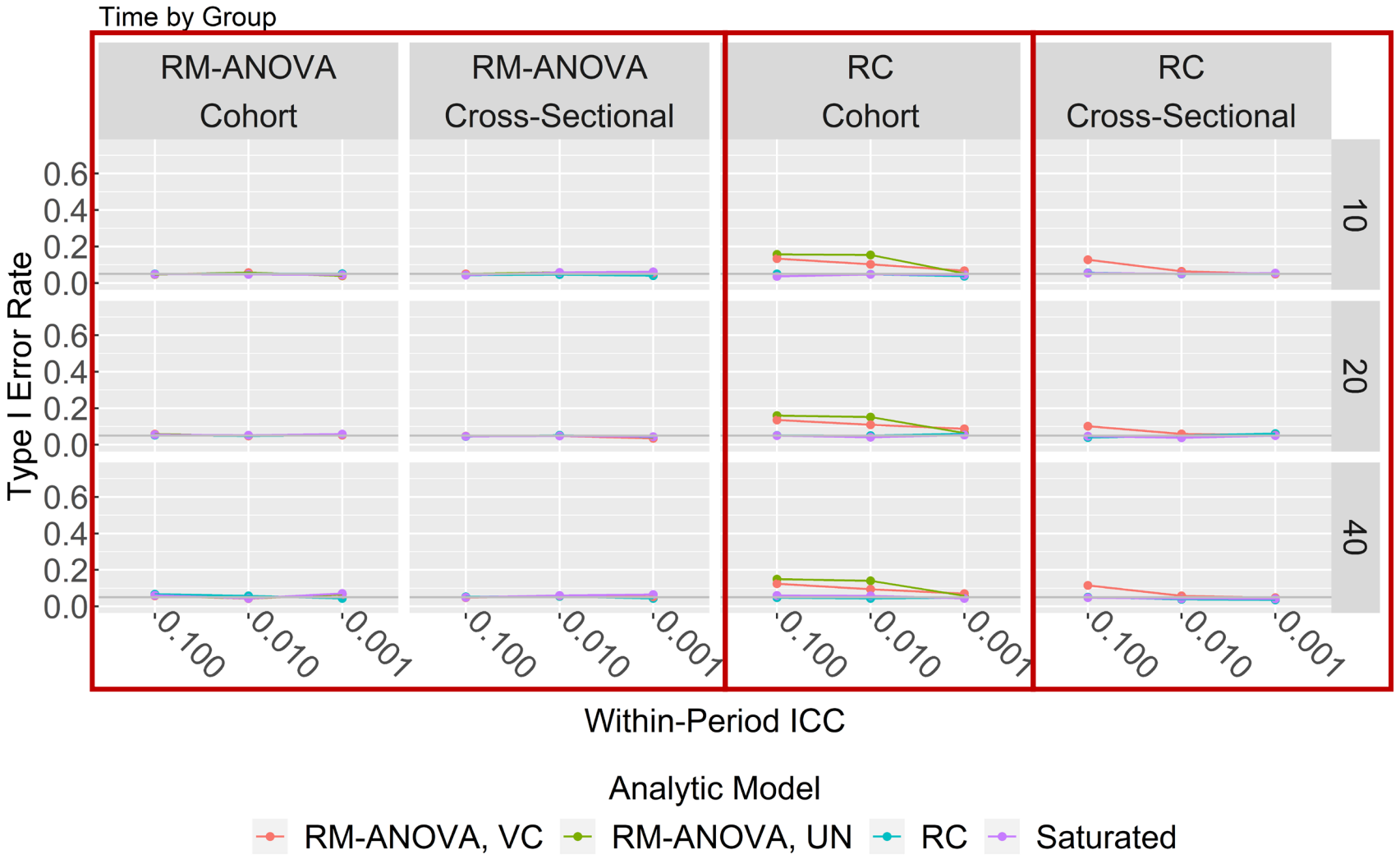
- The four analytic models:
  - RM-ANOVA with VC
  - RM-ANOVA with UN
  - Random Coefficients (RC)
  - Saturated
- These are referred to as “time x group” analytic models.
- Additionally, versions of the RM-ANOVA and RC analytic models omitting time x group random effects were fit.
  - Referred to as “intercept only” models.
- If you recall, data sets were generated assuming time x group random effects.
- Used to address Aim 3:
  - *How important is the time x group random effect term in the analytic model if the data generation mechanism also includes variability at that level?*

Method – Analytic Models

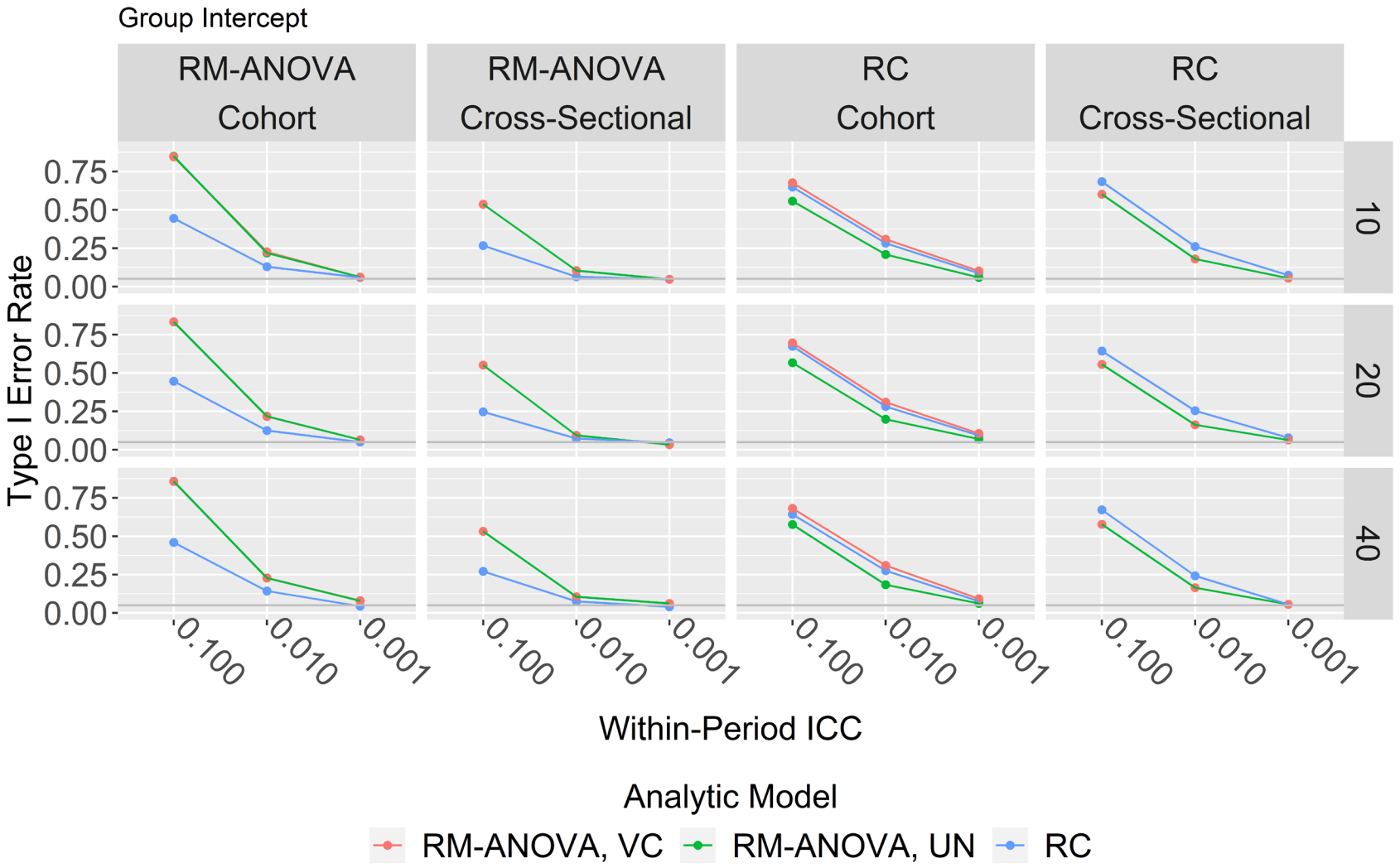
- All analytic models fit using SAS PROC MIXED.
- F-test null hypothesis of no fixed effect time x condition interaction.
  - Has both numerator and denominator degrees of freedom.
- In linear mixed models, denominator degrees of freedom (DDF) must be estimated.
- There are multiple ways to estimate DDF.
  - Differences tend to be minimal if sample sizes are relatively large. (~100 groups)
  - They are more serious with smaller sample sizes, which describes most GRTs.
- We used Kenward-Roger DDF.
  - Performs well in most cases.
- Murray et al. (1998) was under review when the first KR paper was published.

Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. Biometrics. 1997;53(3):983–997.
Kenward MG, Roger JH. An Improved Approximation to the Precision of Fixed Effects from Restricted Maximum Likelihood. Comput Stat Data Anal. 2009;53(7):2583-2595.

Results – Time x Group Analytic Models



Results – Intercept Only Analytic Models



Discussion

Revisiting the three key questions:

1. Would Murray et al. have found better performance with RM-ANOVA analytic models using UN covariance for cross-sectional data?
   - Both RM-ANOVA analytic models with VC and UN covariance structures performed well on RM-ANOVA data.
     - For RM-ANOVA with UN, important to use Kenward-Roger degrees of freedom.
   - RM-ANOVA with UN performed well on RC cross-sectional data, but RM-ANOVA with VC did not unless ICC was low.
   - RC and Saturated analytic models exhibited nominal type I error rates when applied to cross-sectional data.

Discussion

Revisiting the three key questions:

2. Would Murray et al. have seen patterns in cohort data like those they saw with cross-sectional data?
   - RC analytic models maintained nominal type I error rate in cohort data generated under RM-ANOVA and RC mechanisms.
   - Both RM-ANOVA analytic models performed well on RM-ANOVA cohort data.
   - Neither RM-ANOVA analytic model performed well on RC cohort data unless ICC was low.
   - Saturated analytic models maintained nominal type I error rate in cohort data generated under RM-ANOVA and RC mechanisms.

Discussion

Revisiting the three key questions:

3. How important is the time x group random effect term in the analytic model if the data generation mechanism also includes variability at that level?
   - Serious type I error rate inflation was observed unless the ICC was small.

- During review, it was suggested that the analytic models be applied to data generated with a group random effect but no time x group random effect.
  - Little to no impact on type I error rates if time x group random effects were included.
  - Recommend the use of time x group random effects in all cases, as there is potential for a serious problem if omitted.

Conclusions

- RC and Saturated analytic models specifying time x group maintained nominal type I error rate to all data sets generated under a cohort or cross-sectional parallel GRT design.
  - Recommended analytic models for multiple-period GRTs, allowing investigators to choose to model time as categorical or continuous.
- Analytic models specifying only group-level random effects exhibited substantial type I error rate inflation unless the ICC was low.
  - Recommended to always include time x group random effects in analytic models.

Questions?

Key References

- Bell A, et al. Fixed and random effects models: making an informed choice. Quality & Quantity. 2019;53:1051-74.
- Bell ML, Rabe BA. The mixed model for repeated measures for cluster randomized trials: a simulation study investigating bias and type I error with missing continuous data. Trials. 2020;21(1):148.
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