Choosing appropriate analysis methods for cluster randomised cross-over trials with a binary outcome

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What is a cluster randomised cross-over trial?

Cluster randomised trials:
- randomise groups rather than individuals.
- have to account for dependency in sample size calculation and analysis.

Cross-over trials:
- randomised to A/B or B/A.
- subjects act as their own control.
- have clustering of measurements within subjects.
What is a cluster randomised cross-over trial?

Cluster randomised cross-over (CRXO) trials:

- **Groups** of individuals receive **multiple** treatments. Order is randomised.
- Can have same individuals in all periods, different individuals, or a mixture.
What is a cluster randomised cross-over trial?

Example:
• 2 treatments
• 2 treatment periods
• 8 clusters
May have to use cluster randomisation (e.g. intervention acts at group-level).

Lose power by doing this.
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Lose power by doing this.

In a CRXO, have within cluster comparison which may reduce required size of a cluster randomised trial.

But do have to consider chance of treatment carry-over.
Why is the analysis important?

Two sources of clustering:

- correlations in clusters
- correlations in period within cluster

→ Leads to a more complex analysis.

Not handling correlations appropriately could lead to incorrect or misleading results.
Arnup et al. (2016) systematic review of 139 analyses from 91 CRXO trials.

Found that only 10% (14/139) analyses used potentially appropriate methods that account for both cluster and cross-over design elements.
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- Simulation study for binary outcomes from CRXO trial
- Two-period, two-treatment trial design
- Different patients in each period
Simulations: methods of analysis

Logistic hierarchical models:
- **Fixed** cluster effects,
- **Random** cluster effects,
- **Fixed** cluster effects – *random* period within cluster effects,
- **Random** cluster – *random* period within cluster effects.

Cluster-level summary method: linear regression on proportion of events in each period within cluster.
+ various GEEs and weighted cluster-level summary regressions.
Simulations

- Generated data from a random-random hierarchical model.
- 5000 data sets per scenario.

- Fixed-random has convergence problems.
- Hierarchical models — Type I inflated to over 10% for scenarios with few clusters and extra within-period correlation.
- Cluster effects only perform worse than random–random.
Factorial simulations

- Different combinations of within-cluster and within-period correlations.
- Random-random hierarchical model has inflated Type I errors for scenarios with extra within-period correlation and small numbers of clusters.
- Unweighted cluster-level summary regression has good Type I error, but loses power when correlations are high.
Conclusions

- CRXO design can be useful in some settings to increase power compared to a cluster-randomised trial.
- But have more complex analysis.
- Simulations for binary outcome, two-period CRXO trial with different participants:
  - Ignoring extra within-period correlation can lead to inflated Type I errors: should account for this in analysis method.
  - Need to have a large number of clusters to use a random-random-random hierarchical model.
  - Have to consider potential loss of power if using a cluster-level summary method with a small number of clusters — consider this at design stage.
Systematic review

- Median number of clusters 9 (IQR 4-21).
- 58 trials (69% of those with number of periods available) had only 2 periods.
- 27 trials (30%) included same individuals in all periods.
- Only 9% (12/139) analyses performed at cluster-level.
- Out of 127 individual-level analyses, only 4 used potentially appropriate methods. 54 did not account for clustering or cross-over elements. No analyses used random effect for cluster-period.
Simulation parameters

Initial simulation — increasing number of clusters

- 15\% event rate in control arm, first period
- Fixed period effect OR of 0.85
- Cluster ICC 0.062, extra cluster-period ICC 0.023
  \((\sigma_c^2 = 0.137, \sigma_p^2 = 0.081)\)
- Number of clusters 6–80, number of patients per cluster-period 200–8
Simulation parameters

Initial simulation — increasing extra period within cluster correlation

- 15% event rate in control arm, first period
- Fixed period effect OR of 0.85
- Cluster ICC 0.062
  - extra cluster-period ICC 0.001 ($\sigma_c^2 = 0.214, \sigma_p^2 = 0.003$)
  - extra cluster-period ICC 0.005 ($\sigma_c^2 = 0.200, \sigma_p^2 = 0.017$)
  - extra cluster-period ICC 0.01 ($\sigma_c^2 = 0.182, \sigma_p^2 = 0.035$)
  - extra cluster-period ICC 0.05 ($\sigma_c^2 = 0.042, \sigma_p^2 = 0.176$)

- Number of clusters 6 or 30, number of patients per cluster-period 200 or 22 respectively
Simulation parameters — factorial simulations

- 15% or 45% event rate in control arm, first period
- Fixed period effect OR of 0.85 (15% event rate) or 0.92 (45% event rate)
- No treatment effect or OR 0.5 (for 15% event rate) or OR 0.75 (for 45% event rate)
- ICC combinations (cluster ICC, extra cluster-period ICC)
  - 0.023, 0 ($\sigma_c^2 = 0.077, \sigma_p^2 = 0$)
  - 0.062, 0 ($\sigma_c^2 = 0.217, \sigma_p^2 = 0$)
  - 0.023, 0.01 ($\sigma_c^2 = 0.044, \sigma_p^2 = 0.034$)
  - 0.062, 0.023 ($\sigma_c^2 = 0.137, \sigma_p^2 = 0.081$)
- For 15% event rate: 6 clusters, number of patients per cluster-period 200 or 330; or 30 clusters, number of patients per cluster-period 22 or 31
- For 45% event rate: 6 clusters, number of patients per cluster-period 400 or 600; or 30 clusters, number of patients per cluster-period 55 or 75
Note: corresponds to 80%, 90% power for ICC combination 2
Simulation parameters — further simulations

Random–random hierarchical model only

- 15% event rate in control arm, first period
- Fixed period effect OR of 0.85
- No treatment effect or OR 0.5
- ICC combinations (cluster ICC, extra cluster-period ICC)
  - 0.023, 0 ($\sigma_c^2 = 0.077, \sigma_p^2 = 0$)
  - 0.062, 0 ($\sigma_c^2 = 0.217, \sigma_p^2 = 0$)
  - 0.023, 0.01 ($\sigma_c^2 = 0.044, \sigma_p^2 = 0.034$)
  - 0.062, 0.023 ($\sigma_c^2 = 0.137, \sigma_p^2 = 0.081$)
- Number of clusters 6–100, number of patients per cluster-period 200–6
If no extra period within cluster correlation, then size-weighted cluster-level summary method works well.

BUT Type I error is inflated for high values of extra period within cluster ICC.

Same for ICC weighted regression, plus sometimes give negative weights.

None of the GEE models considered in initial simulations had appropriate Type I errors.