Is adding more clusters always more efficient than adding more subjects per cluster?

Andrew Forbes[1] , Kelsey Grantham[1] , Stephane Heritier[1]

John Matthews[2] , Jessica Kasza[1]

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1: Monash University, Melbourne Australia

2: Newcastle University, UK

Outline

- Background – cluster crossover design
- Exponential decay model
- Results
- Discussion/implications

Extending the cluster crossover design AB

Control	Treatment

- Start with the basic AB design
  N clusters, m subjects/period

m	m
m	m

- Double the number of subjects by adding an exact duplicate

m	m
m	m

- Add vertically?

  2N # clusters
  2m per cluster

m	m
m	m
m	m
m	m

ABx2
(long)

- Or add horizontally?
  Double # periods

  N clusters
  4m per cluster

m	m	m	m
m	m	m	m

ABAB
(wide)

A motivating trial question: QUIET trial

- Proposed "QUIET" trial in intensive care
- Cluster crossover trial of noise abatement intervention
- Outcome is hospital length of stay
- Number of clusters (ICUs) is limited
- *Please don't ask about informed consent*

QUESTION:

- Which is more efficient?
  - 4-period ABAB 'wide' design over 2 years
  - a 2-period ABx2 'long' design over 1 year with double the number of clusters.

The 'standard' SW model (Hussey+Hughes 2007)

- $Y_{ijk} = \mu + \pi_j + \beta X_{ij} + \boldsymbol{C_i} + \epsilon_{ijk}$ *k'th person in ith cluster in j'th period*
- $\epsilon_{ijk} \sim N(0, \sigma_\epsilon^2) \quad C_i \sim N(0, \sigma_C^2)$

- $Corr(Y_{ijk}, Y_{ij'k'}) = \rho = \frac{\sigma_C^2}{\sigma_C^2 + \sigma_\epsilon^2}$ for all j, j' , regardless of time distance

$$\begin{pmatrix} 1 & \rho & \rho & \rho & \rho & \rho & \rho & \rho \\ \rho & 1 & \rho & \rho & \rho & \rho & \rho & \rho \\ & & 1 & \rho & \rho & \rho & \rho & \rho \\ & & \rho & 1 & \rho & \rho & \rho & \rho \\ & & & & 1 & \rho & \rho & \rho \\ & & & & \rho & 1 & \rho & \rho \\ & & & & & & 1 & \rho \\ & & & & & & \rho & 1 \end{pmatrix}$$

One cluster
4 periods
m=2/period

Constant variance $\sigma_C^2 + \sigma_\epsilon^2$

Exponential decay model (Kasza et al 2017)

$$Y_{ijk} = \mu + \pi_j + \beta X_{ij} + \boldsymbol{CP_{ij}} + \epsilon_{ijk}$$

- $\boldsymbol{CP_{ij} \sim MVNormal \quad Var(CP_{ij}) = \sigma^2_{CP} \quad Corr(CP_{ij}, CP_{ij'}) = r^{|j-j'|}}$
- $\rho = \frac{\sigma^2_{CP}}{\sigma^2_{CP}+\sigma^2_{\epsilon}}$ = within-period ICC
- Correlation $Corr(Y_{ijk}, Y_{ij'k'}) = \rho r^{|j-j'|}$

$$\begin{pmatrix} 1 & \rho & \rho r & \rho r & \rho r^2 & \rho r^2 & \rho r^3 & \rho r^3 \\ \rho & 1 & \rho r & \rho r & \rho r^2 & \rho r^2 & \rho r^3 & \rho r^3 \\ & & 1 & \rho & \rho r & \rho r & \rho r^2 & \rho r^2 \\ & & \rho & 1 & \rho r & \rho r & \rho r^2 & \rho r^2 \\ & & & & 1 & \rho & \rho r & \rho r \\ & & & & \rho & 1 & \rho r & \rho r \\ & & & & & & 1 & \rho \\ & & & & & & \rho & 1 \end{pmatrix}$$

ρ is 'base correlation'

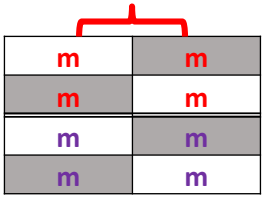
r is 'decay factor'

*Kasza J, Hemming K, Hooper R, Matthews JNS, Forbes A. Impact of non-uniform correlation structure on sample size and power in multiple-period cluster randomised trials. SMMR, 2017 (online)

The QUIET trial – getting plausible values of ρ, r

- Data: Four 6 month periods 2012-2013, 33 ICUs, ANZ administrative dataset
- Average ~700 patients per 6 month period
- Fit exponential decay mixed model to log(Length of Stay)
- $\sigma_{CP}^2 = 0.039,\ \sigma_\epsilon^2 = 1.09 \ \rightarrow \ \hat{\rho} = 0.035$
- $\hat{r} = 0.95 \rightarrow 5\%\ decay$ per period $(decay = 1\text{-r})$

The vertical long design ‘ABx2’



- Treatment effect estimator is simple average of treatment-control in each of the 4 sequences

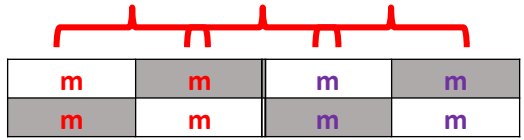
Control	Treatment

- $\hat{\beta}_{ABx2} = \frac{1}{4}[(\bar{Y}_{12} - \bar{Y}_{11}) + (\bar{Y}_{21} - \bar{Y}_{22}) + (\bar{Y}_{32} - \bar{Y}_{31}) + (\bar{Y}_{41} - \bar{Y}_{42})]$

- $Var(\hat{\beta}_{ABx2}) = \frac{\sigma_T^2}{2}\rho\left(\frac{1}{R} - 1 + decay\right)$ $\qquad R = \frac{m\rho}{1 + (m-1)\rho}$

- Variance increases as decay increases, as expected with crossover design
  - Treated and control less correlated within cluster

The horizontal wide design ABAB



Super tedious to derive!

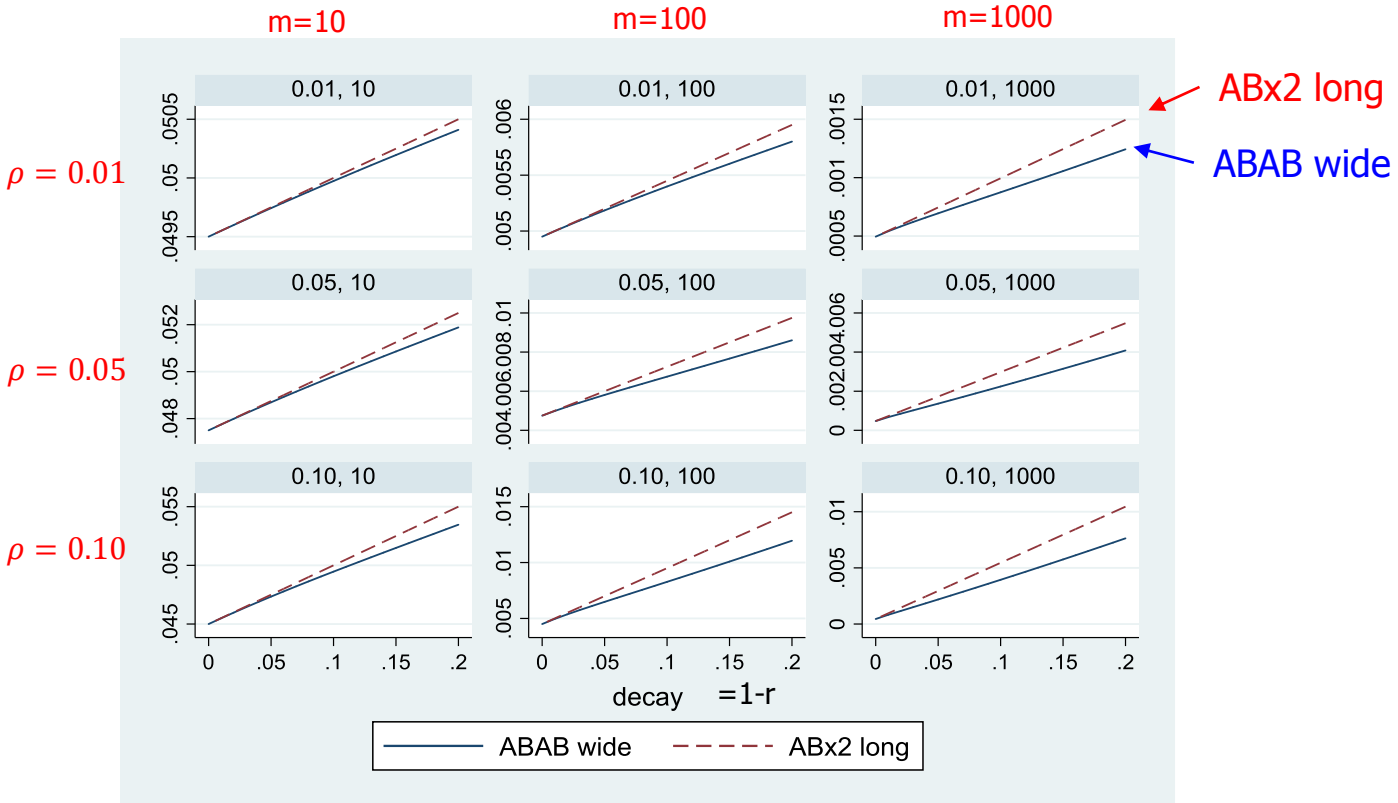
- $\hat{\beta}_{ABAB} = \dfrac{\left(\frac{1}{R}-r^2\right)[\,(\bar{Y}_{12}-\bar{Y}_{11})+(\bar{Y}_{14}-\bar{Y}_{13})]+\left(r-r^3\right)(\bar{Y}_{12}-\bar{Y}_{13})+(same\ for\ seq\ 2)}{2\left(\frac{2}{R}-2r^2+r-r^3\right)}$

= weighted average of adjacent trt-control differences

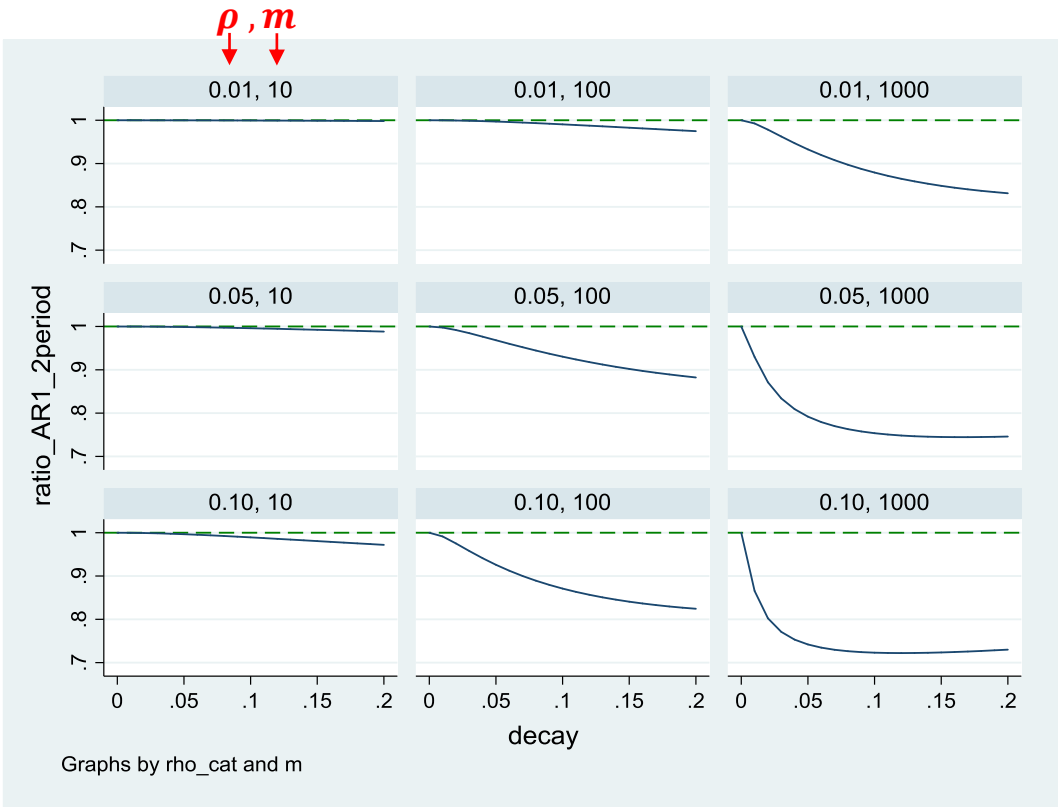
- $\mathrm{Var}(\hat{\beta}_{ABAB}) = \sigma_T^2\ \rho\ \dfrac{1+R^2r^2(2r-1)-Rr\left(1+r^2\right)}{2R-R^2r\left(-1+r(2+r)\right)}$ $\qquad R = \dfrac{m\rho}{1+(m-1)\rho}$

- Variance increases with decay
- Will show graphs!

Graph of variances vs decay. Var(ABAB) < Var(ABx2)!



Does it matter? Relative variance graphs $= \frac{Var(ABAB)}{Var(ABx2)}$



Gains up to 30% with larger m and larger ρ (QUIET gain =15%)

What does this mean? (eg QUIET trial)

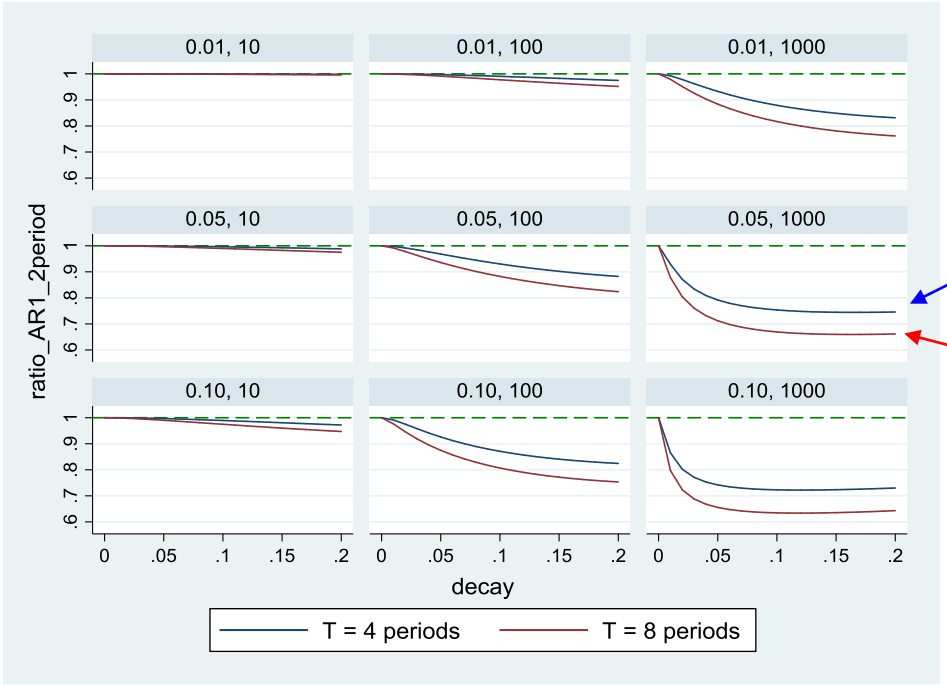
- Eg 15% lower variance with ABAB design compared to ABx2
- → ***15% fewer subjects required***, but same power

- Eg QUIET: if long ABx2 required 80 clusters with 2 periods (1 year), wide ABAB requires 34 clusters with 4 periods (2 years)

Extend to T=8 periods ABABABAB vs long m/period

m	m	m	m	m	m	m	m
m	m	m	m	m	m	m	m

m	m
m	m
m	m
m	m
m	m
m	m
m	m
m	m



4 periods

8 periods

Variance reduction *more pronounced* for T=8 than T=4

How can this be?

- Conventional wisdom in cluster trials is that adding more clusters is more efficient than adding more patients per cluster

→Reason for better efficiency of ABAB is that with exp decay the first trt-control $(\bar{Y}_{12} - \bar{Y}_{11})$ is NEGATIVELY correlated with the second trt-control $(\bar{Y}_{14} - \bar{Y}_{13})$

- $Corr(\bar{Y}_{12} - \bar{Y}_{11}, \bar{Y}_{14} - \bar{Y}_{13}) = -\frac{r(1-r)^2}{2\left(\frac{1}{R}-r\right)} < 0$ [largest when R→1; $m\rho$ large]

→ Adding the second AB in periods 3 and 4 makes the overall variance LESS than the sum of the two AB components

- Var(W+V) = Var(W) + Var(V) + 2*Cov(W,V)

<0

Discussion/Implications

- Main result:
  Crossover with fewer clusters and more periods is more efficient than the two period design
  - Is a non-trivial gain even with small decay if m large
  - Gains are greater with more periods / more switches
  - Jess Kasza Rshiny app: *https://monash-biostat.shinyapps.io/MoreClusters_OR_MorePeriods/*
  - But if correlation fully exchangeable, or Hooper-Girling constant CAC, then zero gain

- *Fewer* clusters
  - Concerns about generalisability
  - variance components unknown so need small sample corrections for estimation

- *More* periods
  - Longer trial duration feasible?
  - many ABABABAB switches: predictable/blinding issues?

- Kelsey Grantham's talk: how many crossovers is optimal with fixed trial duration, continuous recruitment and continuous time decay

Thank you