Stepped-Wedge design effects for unequal clusters

Alan Girling

University of Birmingham, UK

A.J.Girling@bham.ac.uk

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Background: Parallel Cluster Designs

- For clusters of equal size, the standard Design Effect is
$$\text{DE}_0 = 1 + (m - 1)\rho$$
where m = cluster size, ρ is the Intra-cluster correlation (ICC)
- Adjustments for unequal clusters: $m_1, m_2, \ldots m_K$

$$\text{DE} = \text{DE}_0 \div \text{Relative Efficiency (RE)}$$

- Here: $\text{RE} = \Psi\left(m \frac{\rho}{1-\rho} \right)$ where $\Psi(z) = (1+z) \times \frac{1}{K} \sum_{i=1}^{K} \frac{m_i}{m + z m_i}$
- This form leads to an 'exact' Design Effect
$$\text{DE} = mK \left[\sum \frac{m_i}{1 + (m_i - 1)\rho} \right]^{-1}$$
(Refs see Rutterford et al,2015)
- Where exact cluster-sizes are not available, Design Effects can be obtained by approximating the function $\Psi(z)$. (van Breukelen & Candel, 2007)

Approximations using cluster-size coefficient of variation (CV)

1. (Taylor approximation)

$$\Psi_{BC}(z) = 1 - \frac{z}{(1+z)^2}\mathrm{CV}^2$$

– a reliable approximation in many situations (van B & C)

2. (A conservative method, corresponds to the Least Favourable Distribution of cluster-sizes, for given CV)

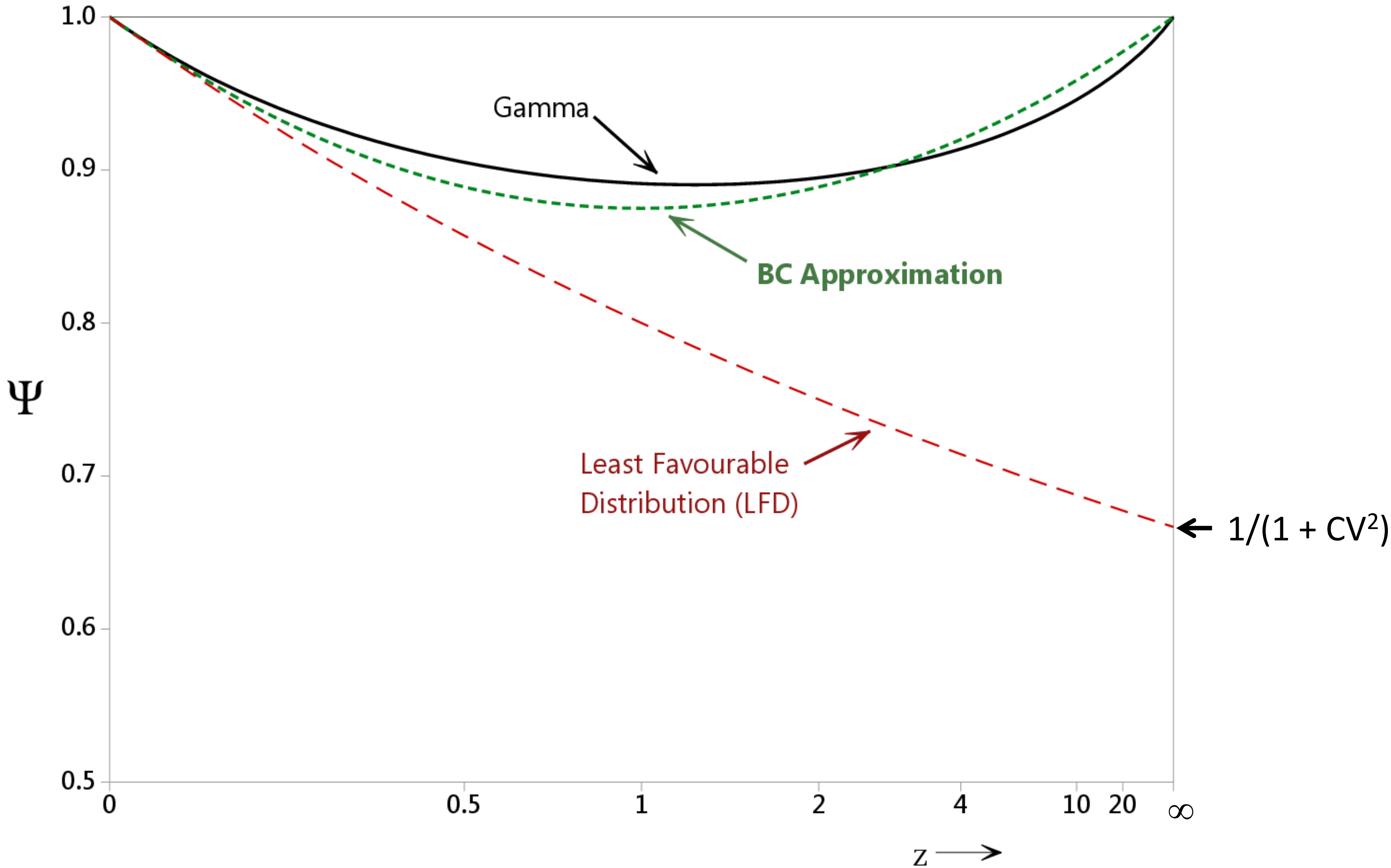
$$\Psi_{LFD}(z) = \frac{1+z}{1+z\left(1+\mathrm{CV}^2\right)}$$

This gives

$$\mathrm{DE} = 1 + \left[m\left(1+CV^2\right) - 1\right]\rho$$

which over-estimates the exact design effect.

RE Function - $\Psi(z)$ - when $CV^2 = ½$



Aims

1. Extension to Stepped-Wedge design layouts
2. Extension to more general correlation structures
   - (Standard model of Hussey & Hughes(2007), single ICC)
   - General exchangeable correlation structure with cluster- and subject-level autocorrelations (Hooper et al, 2016) incorporating Cohort and Cross-sectional sampling.

Design layouts

Time →

Clusters ↑

0	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	0	0	0
1	1	1	1	1	1	1	1	1	1
1	1	1	1	1	1	1	1	1	1

Parallel (PL)

$$\xi = 1$$

0	0	0	0	0	0	0	0	1	1
0	0	0	0	0	0	1	1	1	1
0	0	0	0	1	1	1	1	1	1
0	0	1	1	1	1	1	1	1	1

Stepped-Wedge (SW_g)

$$\xi = \frac{1}{2}\left(1 - \frac{1}{g+1}\right)$$

0	0	0	0	0	1	1	1	1	1
0	0	0	0	0	1	1	1	1	1
1	1	1	1	1	0	0	0	0	0
1	1	1	1	1	0	0	0	0	0

Cross-Over (XO)

$$\xi = 0$$

- Each design here has $T = 10$ measurement periods
- 'Consistency Coefficient': $\xi = \dfrac{T\sum_i \left(\bar{X}_{i\bullet} - \bar{X}_{\bullet\bullet}\right)^2}{\sum_i \sum_j \left(X_{ij} - \bar{X}_{\bullet j}\right)^2}$ measures consistency of treatment incidence over time.

Correlation Structure (from Hooper, 2016)

- ("Intra-cluster Correlation", ICC)
  ρ = correlation between two individuals from the same cluster at the same time
- ("Cluster autocorrelation")
  π = correlation between two population means from the same cluster at different times
- ("Individual autocorrelation")
  τ = correlation between two assessments of the same individual *in a given cluster* at different times
- For Cross-sectional sampling, set $\tau = 0$.
- (Hussey and Hughes model has $\pi = 1$, $\tau = 0$.)
- (BUT no dependence on magnitude of time-difference between measurements..., Kasza et al 2017)

Main Results

- Basic Parallel Design: $\mathrm{RE} = \Psi\left(m\frac{\rho}{1-\rho}\right)$
  $(T = 1)$
- General Parallel Layout: $\mathrm{RE}_{PL} = \Psi\left(\lambda_1 m\frac{\rho}{1-\rho}\right)$ with $\lambda_1 = \frac{1+(T-1)\pi}{1+(T-1)\tau}$
- Cross-Over Layout: $\mathrm{RE}_{XO} = \Psi\left(\lambda_0 m\frac{\rho}{1-\rho}\right)$ with $\lambda_0 = \frac{1-\pi}{1-\tau}$

- Stepped-Wedge: $\mathrm{RE}_{SW} = \alpha\mathrm{RE}_{PL} + (1-\alpha)\mathrm{RE}_{XO}$ $(0 < \alpha < 1)$

$$\left[\alpha = \frac{\nu\xi}{1-\xi+\xi\nu} \text{ with } \nu = \frac{1-\tau}{1+(T-1)\pi}\cdot\frac{1+(m\lambda_0-1)\rho}{1+(m\lambda_1-1)\rho}\right]$$

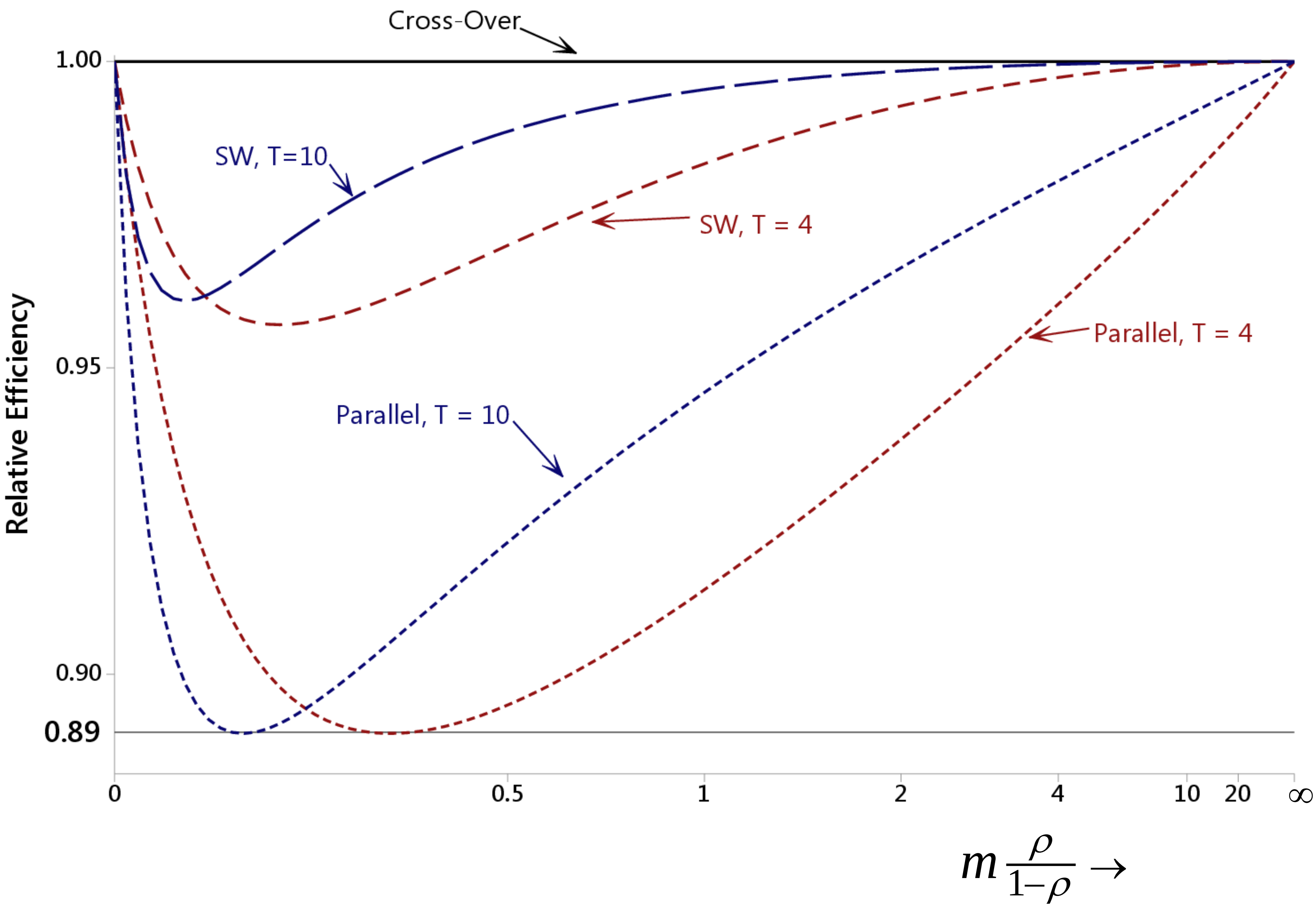
RE Results

- RE_{SW} is a weighted average of RE_{PL} and RE_{XO} and so lies between them

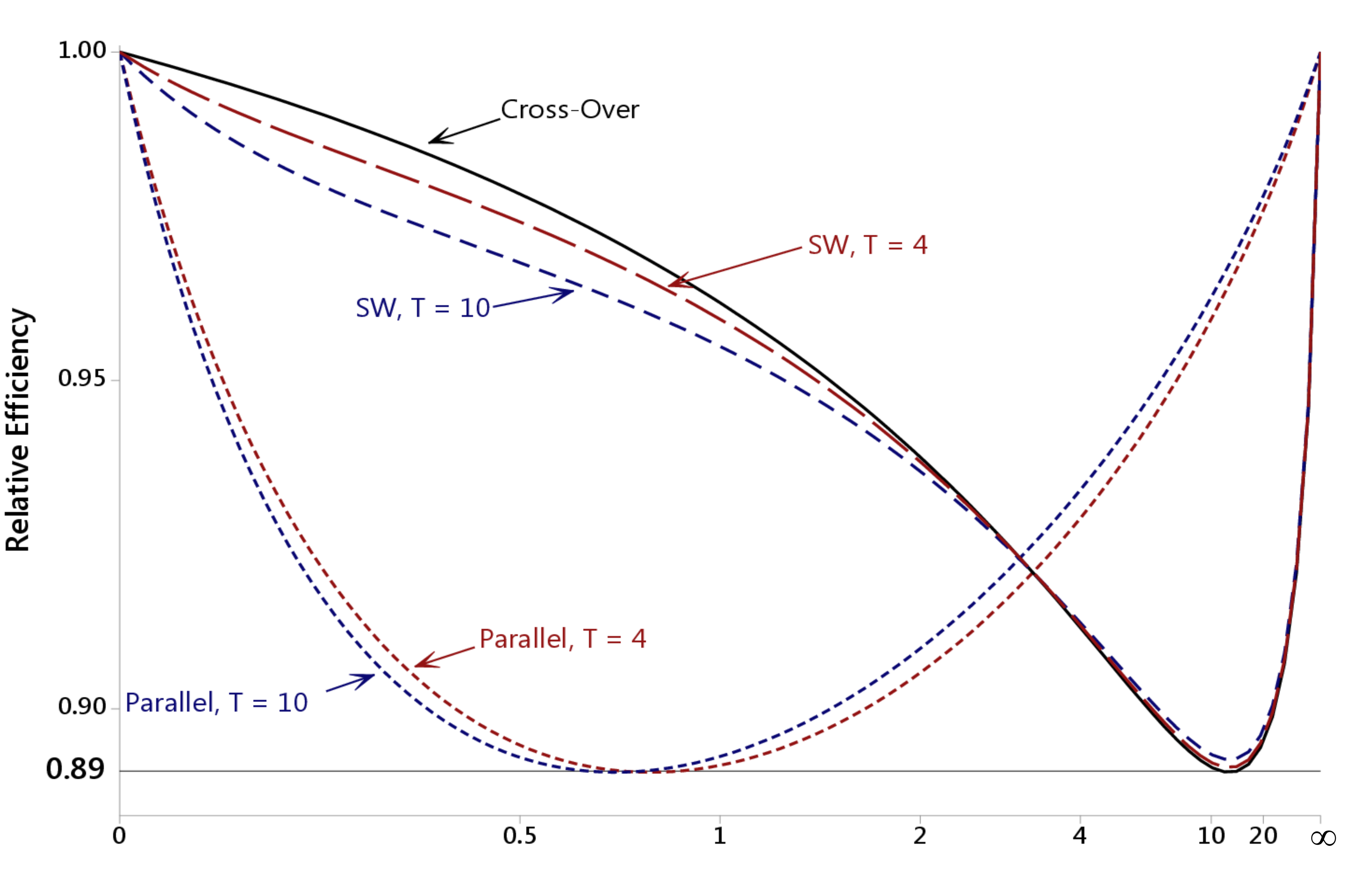
- In the Hussey and Hughes model, $\pi = 1$, $\mathrm{RE}_{XO} = 1$ so that $\mathrm{RE}_{SW} > \mathrm{RE}_{PL}$. Efficiency loss due to unequal clusters is less than for a parallel layout.

- RE_{PL} and RE_{XO} each take the form $\mathrm{RE} = \Psi\left(\lambda m \frac{\rho}{1-\rho}\right)$
  Hence ANY method that works for the basic parallel design can be extended to Stepped-Wedge designs
  - Including BC-approximation, and the conservative LFD method.

Relative Efficiency for π = 1, τ = 0, (H&H model)



Relative Efficiency for $\pi = 0.95$, $\tau = 0.5$



$$m \frac{\rho}{1-\rho} \rightarrow$$

BC-Approximation

- Put $\Psi_{BC}(z) = 1 - \frac{z}{(1+z)^2}\mathrm{CV}^2$ into the general formula

$$\mathrm{RE}_{SW} = \alpha\Psi\left(\lambda_1 m \frac{\rho}{1-\rho}\right) + (1-\alpha)\Psi\left(\lambda_0 m \frac{\rho}{1-\rho}\right)$$

- Minimum value of Ψ_{BC} is $1 - \frac{\mathrm{CV}^2}{4}$.

So $\mathrm{RE}_{SW} \geq 1 - \frac{\mathrm{CV}^2}{4}$ under this approximation.

(88% if $\mathrm{CV}^2 = 0.5$)

LFD Approximation

- I.e. Use $\Psi_{LFD}(z) = \dfrac{1+z}{1+z\left(1+\mathrm{CV}^2\right)}$ in RE expression etc…

- It turns out that this leads to the equal-cluster design effect with m replaced by $m(1 + \mathrm{CV}^2)$ - for all designs, not just the basic parallel layout.
  So equal-cluster technology (e.g. Hooper) can be used to generate a conservative unequal-cluster design effect.

Two Rules of Thumb

- "The loss of efficiency due to variation in cluster sizes rarely exceeds 10%" (van Breukelen, 2007)
  - (from CV = 0.63 in Min Ψ_{BC})
- "When the coefficient of variation is < 0.23, the effect of adjustment for variable cluster size on sample size is negligible" (Eldridge, 2006)
  - (from Ψ_{LFD})
- These rules are based on worst-case scenarios for simple parallel studies and so apply also to stepped-wedge designs.

Emergency Laparotomy Trial (EPOCH)

- Design 6 x SW_{15} : 90 hospitals 16 five-week periods. Average 18 patients per hospital per period.
- Power calculation used Hussey & Hughes model ($\pi = 1$, $\tau = 0$)
- 90-day mortality 25%, with coefficient of variation across hospitals $\approx 0.15 \rightarrow \rho \approx 0.0075$
- Consistency Coefficient: $\xi = 0.8823$
- $\nu = 0.3148$, $\lambda_1 = 16$, $\lambda_0 = 0$, $\alpha = 0.7024$
- $\text{RE} = 0.783 + 0.217 \times \Psi(2.177)$

Power calculation revisited

(For mortality reduction 25% to 22%)

Method	Precision	Power	
Equal Clusters	1.471	95.3%	
Gamma	1.437	94.9%	
LFD	1.389	94.2%	(lower bound)
BC-Approximation	1.436	94.9%	

Impact of unequal clusters is low.

Summary

- Explicit formulae for Relative Efficiency of unequal cluster designs have been given under Stepped-Wedge layouts with cross-sectional or longitudinal sampling and an exchangeable correlation structure.
- The formulae incorporate cluster-size distributions through existing expressions for Parallel designs. Thus methods and approximations developed for such designs can be extended to Stepped-Wedge layouts.
- In general the impact of unequal clusters is likely to be no worse for Stepped-Wedge than for Parallel layouts.

Caveats

- Results obtained under Linear Mixed Model with known correlations
- No time decay allowed – exchangeable correlation structure (excludes time-decaying correlations of Kasza, Hemming et al, 2017)
- Results are exact only when randomisation is stratified by cluster-size
  - Common assumption in existing work on parallel trials
  - Under unrestricted randomisation there will be a distribution of REs – even for a classic parallel design – unless the number of clusters is large
  - An issue for trial design?