BE CAREFUL WHAT YOU ASK FOR:
Stepped wedge trials with time-varying treatment effects

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Background on stepped wedge design and analysis

- Clusters randomized to when intervention is received
- Typically, measure outcome on each cluster, at each time step
- SW often used to measure effectiveness during roll-out

**FIGURE 1** Schematic representations of a parallel CRT versus a stepped wedge CRT design with 8 clusters.
Immediate treatment (IT) model:
(Hussey & Hughes 2007)

\[ Y_{ijk} = \alpha + \beta_j + \delta X_{ij} + \nu_i + e_{ijk} \]
The problem of a time-varying treatment effect

IT model: \[ Y_{ijk} = \ldots + \delta X_{ij} + \ldots \] (1)

ETI model: \[ Y_{ijk} = \ldots + \delta(s_{ij})X_{ij} + \ldots \] (2)

(Kenny et al, 2022)

- In model (2), the treatment effect \( \delta \) is a function of exposure time \( s_{ij} \) (time since intervention start).
Stepped wedge design

Cluster

Time

0 1 2 3 4 5

4
The problem of a time-varying treatment effect

IT model:  \[ Y_{ijk} = \cdots + \delta X_{ij} + \cdots \] \hspace{1cm} (1)

ETI model:  \[ Y_{ijk} = \cdots + \delta (s_{ij})X_{ij} + \cdots \] \hspace{1cm} (2)

(Kenny et al, 2022)

- In model (2), the treatment effect \( \delta \) is a function of \textit{exposure time} \( s_{ij} \) (time since intervention start).
- What happens if data are generated according to (2) but analyzed with (1)?
The problem of a time-varying treatment effect
The problem of a time-varying treatment effect
The problem of a time-varying treatment effect
Analysis of stepped wedge with time-varying treatment effect

So what do we do???
1. Think hard about what you mean by “Treatment effect”
   • Treatment effect at a particular time?
   • Average treatment effect over an interval?
   • Average treatment effect after a lag?

2. Avoid modelling assumptions
Analysis of stepped wedge with time-varying treatment effect

**ETI model**

\[ Y_{ijk} = \cdots + \delta(s_{ij})X_{ij} + \cdots \]

\( \text{ATE estimator: } \hat{\Psi}_{[s_1,s_2]} = \frac{1}{s_2 - s_1 + 1} \sum_{r=s_1}^{s_2} \hat{\delta}(r) \)

\( \text{PTE estimator: } \hat{\Psi}_s = \hat{\delta}(s) \)
Key findings:

- Estimate from IT model is biased for ATE/PTE in all cases, except when IT model is true
- ATE/PTE estimator is unbiased in all cases
- ATE/PTE is less “efficient” (bigger standard error) than IT model estimator when IT model is true
Conclusions:

• In stepped wedge studies, be careful fitting models that assume immediate, constant treatment effect.

• Think carefully about how you want to define the “treatment effect”.

• In most cases, we recommend constructing a robust estimate of the treatment effect based on $\hat{\delta}(s)$. 
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The problem of a time-varying treatment effect

Why does this happen?

- The usual IT estimator can be written as \( \hat{\delta} = \sum_s w(s)\hat{\delta}(s) \)
- \( w(s) \) are weights that sum to 1.0
- BUT \( w(s) \) can be >1 or <0!
  - This can occur when you combine multiple correlated estimators (of the same parameter) that have variable precision
- In the examples given, \( w(1) > 1 \) and \( w(6) < 0 \)
The problem of a time-varying treatment effect

- (a) Instantaneous
- (b) Lagged
- (c) Curved
- (d) Partially convex

Effect curve: Estimated vs. True
Treatment effect is not constant - Power

- Specify the SW design via design matrix $X$ (including time-varying treatment effect)
- Use GLMM framework to specify variance $\Sigma$
- Specify the estimator $\hat{\Psi} \equiv \frac{1}{s_2 - s_1 + 1} \sum_{r=s_1}^{s_2} \hat{\delta}_r$

$$Var(\hat{\Psi}) = H^T (X^T \Sigma^{-1} X)^{-1} H$$

For testing $H_0: \Psi = 0$,

$$Power(\Psi) = \Phi \left( \sqrt{\frac{\Psi^2}{Var(\hat{\Psi})}} - Z_{1-\frac{\alpha}{2}} \right)$$