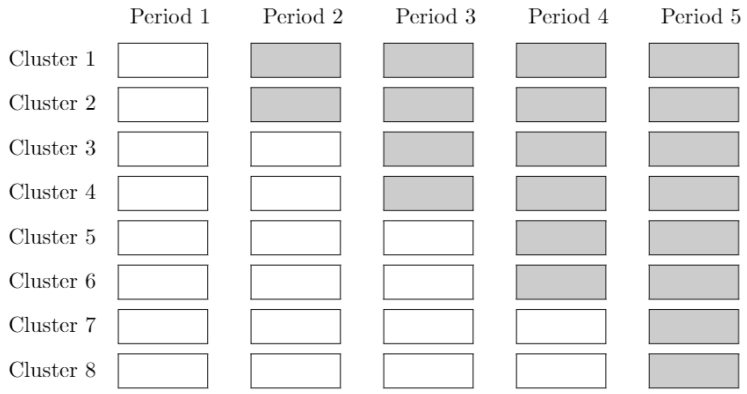
Recent Developments in Statistical Methods for Pragmatic, Stepped Wedge Cluster Randomized Trials

Plenary Address by Fan Li, PhD

A **Stepped Wedge Cluster Randomized Trial** (SW-CRT) uses a design that allows for phased implementation of an intervention. In a SW-CRT, clusters are randomized to intervention sequences that differ by the time points when the intervention starts to roll out. There are three major types of SW-CRTs, **cross-sectional, closed-cohort and open-cohort**, depending on whether the same set of participants are followed over time. As in a Parallel-Arm CRT, cluster randomization leads to positively correlated individual responses, both within and between time periods. Appropriate statistical methods (such as mixed models or GEE) should be considered for design and analysis.



The **advantage** of SW-CRTs is logistical convenience. Another attractive feature is that all clusters eventually receive the intervention, which can help facilitate recruitment when cluster stakeholders perceive the intervention to be beneficial. The **challenge** of SW-CRTs is that it may take longer to finish, and requires additional data collection effort (for example, in a closed-cohort design).

Unlike in a Parallel-Arm CRT, the design and analysis of SW-CRTs are mostly model-based, and requires accounting for secular trend and more complex **intraclass correlation coefficients** (ICCs). For example, the essential ingredient of a mixed model expresses the mean outcome as the sum of [secular trend] + [intervention effect] + [heterogeneity]. Variations of each components exist to address different complications arising from SW-CRTs. Different specifications of the [heterogeneity] component induces different ICC structures, that differentiates **within-period ICC, between-period ICC,** and **longitudinal autocorrelation,** depending on specific design variant. Compared to Parallel-Arm CRTs, sample size determination in SW-CRTs requires more ICC parameters as well as sensitivity analysis. Software tools are available in SAS, R and Stata to facilitate these calculations.

Analysis of SW-CRTs should adequately adjust for secular trend and ICC structures. Two mainstream model-based approaches are **conditional models (mixed models)** and **marginal models (GEE),** the latter of which carries a straightforward **population-averaged** interpretation. Software for mixed models is widely accessible, whereas more advanced tools for GEE analysis of SW-CRTs has been recently developed to address computational challenges with large cluster sizes and complex ICC structures. It is strongly advocated to estimate ICCs in analyzing SW-CRTs, for better reporting practice as well as efficiency considerations.

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