Invited sessions for ISCB42 (Lyon, 2021)
Session 8

Optimal design of longitudinal cluster randomised trials

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Dr Jess Kasza : School of Public Health and Preventive Medicine, Monash University, Australia
Faster and more agile designs: speeding up the stepped wedgewith batched designs

Prof Richard Hooper : Institute of Population Health Sciences, Queen Mary, University of London, UK Longitudinal cluster randomised trials with continuous recruitment

Dr Andrew Copas : University College London, UK
Optimal design of cluster randomised trials with baseline measurements

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Faster and more agile designs: speeding up the stepped wedge with batched designs

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Stepped wedge designs are an increasingly popular variant of longitudinal cluster randomised trial designs. Stepped wedge designs roll interventions out across clusters in a randomised, but step-wise fashion, and gain power over standard cluster randomised trials through within-cluster comparisons. However, the standard stepped wedge design is typically neither fast nor agile. All clusters must start and end trial participation at the same time, implying that ethics approvals and data collection procedures must be in place in all clusters before a stepped wedge trial can start in any cluster. Hence, although stepped wedge designs are useful for testing the impacts of many cluster-based interventions on outcomes, this requirement means that there can be lengthy delays before a trial can commence.

In this talk we will discuss the "batched" stepped wedge design. Batched variants of stepped wedge designs allow for clusters to come on-line to the study in batches, instead of all at once, and thus can be deployed more quickly. However, like the stepped wedge, the batched step wedge rolls the intervention out to all clusters in a randomised and step-wise fashion. Provided that the effect of time is appropriately included in the regression model for the outcome, sample size calculations are straightforward and the power of the study will be robust to delays with the start-up of batches. Researchers can also modify sample size calculations to accommodate adaptations such as early stopping for futility or success, or for sample size re-calculation.

Longitudinal cluster randomised trials with continuous recruitment

Richard Hooper

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When a stepped wedge or other longitudinal cluster randomised trial recruits/identifies a consecutive sample of participants from a continuous stream presenting at clusters over a given calendar period, it is quite a different prospect to sampling in a series of discrete, cross-sectional slices. For one thing, introducing an intervention mid-stream to a cluster could contaminate participants recently recruited under the routine care condition. For another, it is inadequate to speak of distinct time "periods": two individuals recruited at either end of the "same" period may have less in common than two individuals recruited just on either side of a "division" between periods. A continuous timescale also offers a continuously adaptable framework for designing a longitudinal trial: timing when to intervene, and when to start or stop recruitment.

This talk focuses particularly on maximising statistical efficiency in two very different design problems. In the simple case of a trial randomising clusters to two groups, intervention and routine care, with an initial, prospective baseline period during which all clusters receive routine care, I show how close-to-optimal efficiency is generally obtained either with no baseline period at all, or with a baseline period that divides the available time in half. This finding is robust to the form of the underlying, fixed effect of time, assuming this is correctly specified in the analysis model (I hope to have simulation results looking at how well different approaches to analysis fare under mis-specification.)

At the other end of the spectrum of design complexity is the case of a longitudinal cluster randomised trial where we choose when each cluster crosses from routine care to the intervention along a continuous timescale, and try to achieve the required statistical power by recruiting the smallest number of participants out of the total presenting at all clusters over the calendar period – an incomplete stepped wedge design. Search algorithms identify surprising solutions – in some instances resembling a series of before-and-after studies rather than concurrent comparisons of intervention and control – though for a design robust to the form of the underlying time effect a smooth "staircase" design may be preferable.

Optimal design of cluster randomized trials with baseline data comparing routine care to a new intervention

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Background: In cluster randomised trials (CRTs) it is sometimes possible to choose a different cluster size (number of individuals measured per cluster) between trial arms, or between baseline and endline e.g. in the SNEHA-TARA trial where clusters are large communities and only a sample of individuals are surveyed. In most trials clusters can be allocated unequally to arms if desired. An optimal design minimises the total number of measurements required for a given number of trial clusters. For CRTs with cross sectional data and a continuous outcome, it is known how to (i) optimally allocate measurements between baseline and endline when the cluster autocorrelation (CAC) is the same across trial arms [1], and (ii) optimally allocate clusters and measurements when the variance or intra-cluster correlation coefficient (ICC) are affected by the intervention [2].

Objective: To extend previous work to trials comparing routine care to a new intervention, assuming a similar ICC and variance for both trial arms at baseline and in the routine care arm at endline, that the intervention is likely to reduce the CAC, and may affect the ICC and variance.

Results: We present algebraic results, and graphical methods, to help identify optimal desgns for this setting. The reduction in number of measurements required compared to the standard design, where clusters are allocated equally to arms and the cluster size is equal over time and between trial arms, can be substantial where cluster sizes or ICC values are large. If the intervention reduces the CAC, but does not affect the variance or ICC, then the optimal design will typically involve (i) smaller cluster size in the intervention arm compared to rountine care at both baseline and endline, and (ii) more clusters allocated to the intervention arm.

Conclusions: Optimal designs can save resources but designs must be chosen to maintain power across plausible ranges for the correlation and variance parameters which will often be wide. We recommend trialists report these parameters separately by arm to inform the design of future trials.

References:

1. Copas AJ, Hooper R Cluster randomised trials with different numbers of measurements at baseline and endline: sample size and optimal allocation. *Clin Trials* 2020 17:69-76
2. Copas AJ, Hooper R Optimal design of cluster randomised trials allowing unequal allocation of clusters and measurements *Stat Med* Under revision