

Stepped wedge trials with continuous recruitment require new ways of thinking

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Introduction

Stepped wedge trials are cluster randomised trials in which clusters are followed longitudinally, with different clusters randomised to cross from the control condition to the active intervention condition at different times.¹ This experimental approach mirrors the natural process of implementing an intervention over many sites, and is often associated with situations where a policy decision has already been made to roll out an intervention.² Stepped wedge trials are increasingly popular, with systematic reviews showing an exponential growth in the number of published reports and registered protocols.²⁻⁷ A new CONSORT extension covering stepped wedge trials has been produced.^{8,9} Methodologists have also embraced the topic: in the pages of the *Journal of Clinical Epidemiology* a vigorous debate blossomed over the relative efficiency of stepped wedge and more traditional designs.^{2,10-21} This discussion illustrated, above all, that precision is key in discussing the unique features of stepped wedge trials: the devil is in the detail.

But the general definition of a stepped wedge trial given above hides substantial variation in their design in practice, according to the plan for recruitment and the flow of individual participants through the study.²² One common subtype involves the continuous recruitment of participants from each cluster over the same interval of time, with different clusters crossing over to the intervention at different points along this interval. For example, in their stepped wedge trial of placental growth factor testing to assess women with suspected pre-eclampsia, Duhig and colleagues recruited participants continuously over a 16-month interval, as and when women presented with suspected pre-eclampsia at one of 11 participating maternity units.²³ This is in sharp contrast to the way data are collected for a trial such as the Devon Active Villages Evaluation (DAVE) by Solomon and colleagues, in which participants were sampled from village communities in a series of discrete cross-sectional surveys.²⁴

The literature on stepped wedge trials has tended not to differentiate too closely between continuous recruitment and discrete sampling. Here we argue that a deeper understanding of the unique features of continuous recruitment processes will help researchers to identify risks of contamination and to make more appropriate design and analysis choices.

Continuous recruitment with short exposure

If participants remained exposed to a potential intervention in the cluster for a long period following their recruitment, then we could follow individuals longitudinally to see how their outcomes change when the cluster crosses from the control to the intervention. But more commonly participants who are recruited continuously are exposed only briefly, and each participant's primary outcome is assessed just once: either as a control or an intervention participant. In the typology of Copas and colleagues this is known as a continuous recruitment short exposure design.²²

For example, Poldervaart and colleagues evaluated a policy which promoted the use of a scoring system to guide clinical decisions for patients with acute chest pain on arrival at hospital emergency departments.²⁵ Nine hospitals were randomised to change over to the intervention at staggered intervals over a recruitment period which ran from July 2013 to August 2014. The primary outcome, assessed for each individual participant, was a major cardiac event within six weeks of presentation at the hospital. Median length of stay in the emergency department (exposure) was 4 hours.²⁶

A note on our terminology: the "exposure" period refers to the interval over which a participant is exposed to the possibility of receiving the active intervention if it were introduced at a cluster – either exposed directly, because the intervention is delivered at cluster level, or indirectly, through contact with other individuals in the same cluster who receive the intervention.

It is worth noting that in a continuous recruitment short exposure design the outcome may be assessed some considerable time after the individual was recruited. The first ever stepped wedge trial, which evaluated the effectiveness of adding Hepatitis B virus (HBV) vaccination to a routine programme of childhood vaccination in The Gambia, provides an extreme example. Clusters were distinct geographical regions defined by the locations of 17 health centres. The schedule of vaccinations lasted for 9 months, but the window of opportunity for a child to be recruited into the trial, and for vaccination of a child to begin, was short (the first month after birth). If a child did not receive HBV vaccination at the first vaccination visit they did not receive it at any subsequent visit. The primary outcome of hepatocellular carcinoma was not determined until 30 years later.²⁷ Even though participants might have lived in the same region of The Gambia for all of those 30 years, their direct “exposure” was short (one month), because of the short window of opportunity for starting HBV vaccination. Thus participants could reliably be labelled as “control” or “intervention” depending on whether they were born before or after the cross-over in their cluster. (The question of indirect exposure is less clear: all participants might have benefitted from some degree of herd immunity over the decades which followed the introduction of the HBV vaccination programme to their communities.)

Contamination within a cluster

In many trials with continuous recruitment it is not possible to cross seamlessly and instantaneously from recruitment under the control condition to recruitment under the active intervention condition. In a cluster in the process of crossing over from the control to the intervention, some participants may experience a mixture of the two, or something intermediate. The CONSORT extension to stepped wedge trials warns of the dangers of this kind of “contamination” of treatments.⁸ To understand these issues in more detail (the devil is in the detail!) we must map out the timeline for cross-over in a cluster. We start by defining terms, and then give examples.

In a stepped wedge trial the cross-over is unidirectional – from the control condition (usually routine care) to the active intervention, but never in reverse. With this kind of unidirectional cross-over there are (up to) four key phases in a cluster: (1) a period of recruitment under the control condition, (2) a period allowing for the “closure” of the control recruitment period (we elaborate on this below), (3) a period of implementation of the active intervention; (4) a period of recruitment under the active intervention.

The closure period (2) should be long enough that any participants who were recruited before the closure period begins will *either* have had their outcomes assessed, *or* are no longer exposed by the end of the closure period. The closure period is therefore the shorter of the exposure period and the time from recruitment to outcome measurement. The implementation period (3) should be long enough for the intervention to be set up within a cluster and operating at full strength.

The closure period is often negligible (or at least short) because exposure is short. In Poldervaart’s trial the amount of time spent by each participant in the emergency department was a tiny fraction of the overall recruitment period. But this is not always the case. Berdal and colleagues reported results from a stepped wedge trial of an experimental rehabilitation programme for patients with rheumatic diseases who were admitted to rehabilitation centres in Norway.^{28,29} The comparator was traditional rehabilitation, whose duration could vary between 1 and 4 weeks, and outcomes were not assessed until after a participant had been discharged. The closure period required for this trial would have been 4 weeks – long enough to ensure that all participants recruited under the control condition had left the centre before the implementation of the intervention began.

The implementation period is also often assumed to be negligible. This is sometimes achieved in practice by delivering training materials to a cluster before the scheduled switch. In Berdal’s trial, for

example, a team of research intervention facilitators visited each centre with study materials 2 weeks before the cross-over was due. It is vital to understand whether intervention materials pre-delivered in this way could be accessed by health professionals or participants in a cluster before the official cross-over. If they can, then the implementation period (as we define it here) must be considered to begin from this point. Other trials have included explicit implementation periods in their design: Peden and colleagues allowed a 5-week interval for their quality improvement intervention to be introduced in hospitals performing emergency laparotomies.³⁰

Avoiding contamination

To avoid contamination we propose the following as a standard of good practice: that all recruitment be suspended for the combined duration of the closure period and implementation period, or at least that these participants be excluded from the primary comparison of control and intervention. This principle was followed in Peden's trial, for example. The combined closure and implementation period is sometimes referred to as a "transition period" between recruitment under the control and intervention conditions.¹

The closure period ensures that outcomes of "control" participants are not contaminated by the intervention, even while it is being set up. The implementation period ensures that "intervention" participants are never receiving a less-than-full-strength intervention – *i.e.* are not contaminated by a weaker form of the intervention.

Diagrams

The CONSORT extension recommends diagrams as a tool for understanding the risk of contamination in stepped wedge designs.⁸ If the phases of control recruitment, closure,

implementation, and intervention recruitment in a cluster are non-overlapping (as we recommend) they can be shown schematically as a sequence of differently shaded or coloured bars running along a time axis. The number of people recruited under the control (or intervention) condition in a given cluster will be the product of the recruitment rate and the length of the control (or intervention) recruitment period. In some situations, as noted above, the closure or implementation period may be assumed to be negligible, meaning that a cluster can cross seamlessly from control recruitment to intervention recruitment. When such an assumption is made it should be justified. If a cluster is not required to include any control participants then a closure period is unnecessary, and the cluster can begin in the implementation or intervention recruitment phase.

Figure 1 illustrates such a diagram for a complete stepped wedge trial design with clusters randomised to four different sequences. The example is a traditional stepped wedge, with cross-over times regularly spaced across sequences, and all clusters starting in the control condition and finishing in the intervention condition. When recruitment is a continuous time process it is worth bearing in mind that we have the freedom to choose cross-over times anywhere along the continuous time-line, and the time selected for one cluster to cross over need not have any significance in another cluster. Nor is there any particular reason for the end of one transition to align with the beginning of another. As long as we have allowed sufficient time for closure and implementation we can usefully begin recruitment again. Observe how different this is to the way time is conceived in the classic Hussey and Hughes model for stepped wedge trials, where time consists of discrete periods divided by cluster cross-overs.³¹

What every stepped wedge trial does require is a fine degree of control over which clusters make the transition to the active intervention and when. This is one of their enduring challenges.

Time as a continuous variable

The analysis of any stepped wedge trial must adjust appropriately for time, which will generally be confounded with treatment (as time goes on more and more clusters are in the intervention condition). Adjusting for time as a discrete factor, as in the Hussey and Hughes model, seems an inadequate approach to the analysis of a stepped wedge trial with continuous recruitment. An alternative might be to model time as a continuous variable with a linear or smoothly varying effect on outcome, rather like an interrupted time series analysis.^{32,33} This kind of analysis choice feeds back to design and sample size calculation: the sample size needed for an analysis adjusting for a continuous, linear effect of time will not be the same as that needed if the adjustment is for discrete time.³⁴

The Hussey and Hughes model also assumes that the intraclass correlation – the correlation between the outcomes of two individuals from the same cluster – is the same for any pair of individuals. This is known as complete exchangeability. Other authors have attempted to generalise this to allow the intraclass correlation to grow weaker over time, while still treating time as discrete.^{35–37} In these discrete-time models for intraclass correlation there is still exchangeability within a given time period. Again, as soon as we view recruitment as continuous this approach becomes inadequate: two individuals recruited at either end of the “same” period will have much less to do with each other than two individuals recruited just on either side of a “division” between periods. An approach where the intraclass correlation decays as a continuous function of the time separating the two individuals may be a better alternative.³² Again, this impacts on design as well as analysis.

Terminology

Copas and colleagues identified three distinct subtypes of stepped wedge trial: continuous recruitment short exposure designs, “open cohort” designs like the DAVE trial with its repeated survey samples, and “closed cohort” designs which follow the same individuals longitudinally.²² Other authors blur the boundaries of open cohort and continuous recruitment designs to form a single category of “cross-sectional” stepped wedge trials, in which each participant is only assessed once.^{1,21} This usage is misleading: “cross-sectional” conjures an image of a series of cross-sectional slices through time – something quite different to a continuous recruitment process. We suggest that the term “repeated cross-section” be restricted to trials involving discrete surveys of a cluster population. We prefer to use the term “continuous recruitment” for what it is. “Continuous recruitment short exposure” is a more specific term, but as noted above the exposure need not always be short.

Conclusions

Continuous recruitment stepped wedge trials are likely to continue to be popular with researchers. Depending on how such a trial is conducted there can be a risk of contamination within a cluster, though some care and thought can help to address this. A diagram can help us to visualise the design and judge the risk more clearly.

We have proposed a diagram describing the timeline of recruitment and transition as planned in advance of a trial. In reality, individual clusters may deviate from the planned timeline. There could also be systematic deviations if, for example, the intervention takes longer to implement than anticipated. By careful monitoring of trial conduct it may be possible to report the actual timelines experienced by clusters, as well as those planned, and to consider the consequent risks of

contamination. Exactly what we mean in general by “intention-to-treat” or “as treated” analyses of a stepped wedge trial may be open to debate,⁸ but with clarity of reporting and reflection on the risks of bias we can start to explore such alternatives.

Though framed in terms of stepped wedge trials, the ideas presented here apply equally to simpler designs for cluster randomised trials with continuous recruitment, such as a parallel groups design with a baseline period. We have not touched on the question of optimal design: how should a schedule be chosen for transition and recruitment to minimise the total number of clusters or participants? This is a fertile area for future research. Incorporating time as a continuous variable in the analysis of stepped wedge trials is also likely to be the focus of ongoing work. Sample size calculation and other design tools need development and expansion in parallel. A continuous timescale gives a stepped wedge trial something of the feel of an interrupted time series study, albeit a randomised one, and perhaps there is more to be learned about the analysis of continuous recruitment stepped wedge trials from a cross-fertilisation with the interrupted time series literature.

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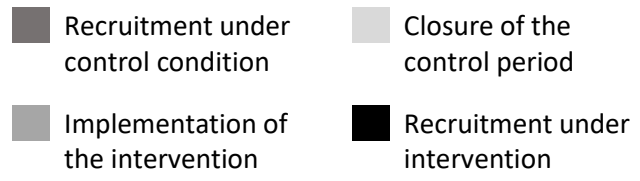
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Figure 1. Schematic representation of a stepped wedge trial with continuous recruitment, distinguishing four phases in each cluster: recruitment under the control condition, closure of the control recruitment period, implementation of the active intervention, and recruitment under the active intervention condition.



Time →

