Methods: Mind the Gap

Webinar Series

Designing Stepped Wedge Trials with Continuous Recruitment

Presented by:

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NIH National Institutes of Health

Office of Disease Prevention

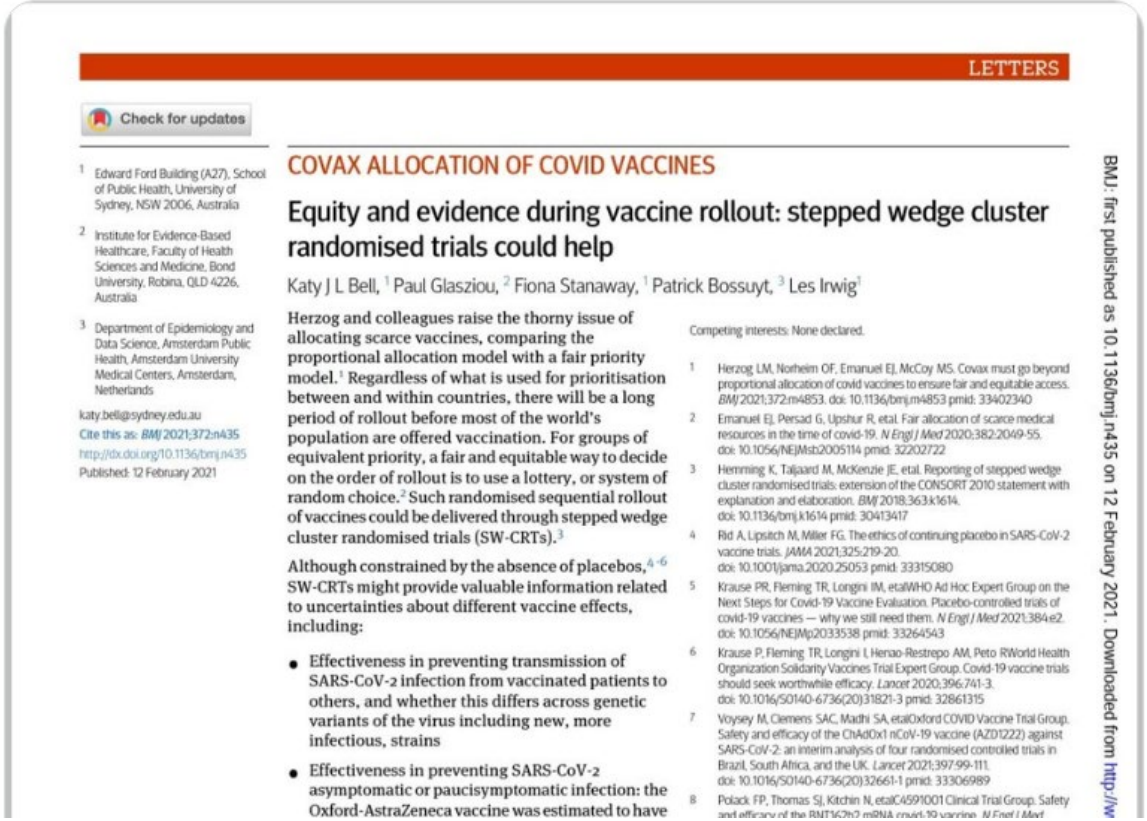
Contents

- Introduction
- New ways of thinking for trials with continuous recruitment
- Some methods
- Some design problems
  - Cluster randomised trials with a prospective baseline
  - Complete stepped wedge trials
  - Incomplete stepped wedge trials
- Concluding remarks

Introduction

Katy Bell
@KatyJLBell

Equity and evidence during vaccine rollout: stepped wedge cluster randomised trials could help bmj.com/content/372/bm...



LETTERS

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COVAX ALLOCATION OF COVID VACCINES

Equity and evidence during vaccine rollout: stepped wedge cluster randomised trials could help

Katy J L Bell,[1] Paul Glasziou,[2] Fiona Stanaway,[1] Patrick Bossuyt,[3] Les Irwig[1]

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[2] Institute for Evidence-Based Healthcare, Faculty of Health Sciences and Medicine, Bond University, Robina, QLD 4226, Australia
[3] Department of Epidemiology and Data Science, Amsterdam Public Health, Amsterdam University Medical Centers, Amsterdam, Netherlands
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Herzog and colleagues raise the thorny issue of allocating scarce vaccines, comparing the proportional allocation model with a fair priority model.[1] Regardless of what is used for prioritisation between and within countries, there will be a long period of rollout before most of the world's population are offered vaccination. For groups of equivalent priority, a fair and equitable way to decide on the order of rollout is to use a lottery, or system of random choice.[2] Such randomised sequential rollout of vaccines could be delivered through stepped wedge cluster randomised trials (SW-CRTs).[3]

Although constrained by the absence of placebos,[4-6] SW-CRTs might provide valuable information related to uncertainties about different vaccine effects, including:

- Effectiveness in preventing transmission of SARS-CoV-2 infection from vaccinated patients to others, and whether this differs across genetic variants of the virus including new, more infectious, strains
- Effectiveness in preventing SARS-CoV-2 asymptomatic or paucisymptomatic infection: the Oxford-AstraZeneca vaccine was estimated to have

Competing interests: None declared.

1 Herzog LM, Norheim OF, Emanuel EJ, McCoy MS. Covax must go beyond proportional allocation of covid vaccines to ensure fair and equitable access. *BMJ* 2021;372:m4853. doi: 10.1136/bmj.m4853 pmid: 33402340
2 Emanuel EJ, Persad G, Upshur R, et al. Fair allocation of scarce medical resources in the time of covid-19. *N Engl J Med* 2020;382:2049-55. doi: 10.1056/NEJMsb2005114 pmid: 32202722
3 Hemming K, Taljaard M, McKenzie JE, et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. *BMJ* 2018;363:k1614. doi: 10.1136/bmj.k1614 pmid: 30413417
4 Rid A, Lipsitch M, Miller FG. The ethics of continuing placebo in SARS-CoV-2 vaccine trials. *JAMA* 2021;325:219-20. doi: 10.1001/jama.2020.25053 pmid: 33315080
5 Krause PR, Fleming TR, Longini IM, et alWHO Ad Hoc Expert Group on the Next Steps for Covid-19 Vaccine Evaluation. Placebo-controlled trials of covid-19 vaccines — why we still need them. *N Engl J Med* 2021;384:e2. doi: 10.1056/NEJMp2033538 pmid: 33264543
6 Krause P, Fleming TR, Longini I, Henao-Restrepo AM, Peto RWorld Health Organization Solidarity Vaccines Trial Expert Group. Covid-19 vaccine trials should seek worthwhile efficacy. *Lancet* 2020;396:741-3. doi: 10.1016/S0140-6736(20)31821-3 pmid: 32861315
7 Voysey M, Clemens SAC, Madhi SA, et alOxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021;397:99-111. doi: 10.1016/S0140-6736(20)32661-1 pmid: 33306989
8 Polack FP, Thomas SJ, Kitchin N, et alC4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine. *N Engl J Med*

Dr. Bertha Hidalgo @berthahidalgo · Jan 19
I just want to know why we have zero randomized trials on dresses with pockets.

135 275 3,496

Dr. Catherine Bulka @DrCatherineB · Jan 19
Double-blinding would be a real problem because whenever complimented on a dress with pockets, the automatic response is always "thanks, it has POCKETS!"

2 112

Eric Lofgren
@GermsAndNumbers

Replying to @DrCatherineB and @berthahidalgo

Stepped wedge design. Eventually, all dress wearers get pockets.

We have the methods to address this balancing ethics and statistical efficiency.

2:27 AM · Jan 19, 2022 · Twitter Web App

What is a stepped wedge trial?

- Usually cluster randomised
- Clusters are randomised, not to one treatment condition or another, but to a ***sequence*** of treatment conditions over an extended interval of time
- In a sequence, cross-over is ***unidirectional***: you cannot cross from the intervention condition back to the control condition

What are the advantages of a stepped wedge trial?

Reputed advantage:

- Everyone gets the intervention

What are the advantages of a stepped wedge trial?

Real advantages are two-fold:

- Statistical efficiency (in some cases)
- Practicality: there may not be “enough” of the intervention to deliver to half the clusters simultaneously

[CANCER RESEARCH 47, 5782–5787, November 1, 1987]

The Gambia Hepatitis Intervention Study[1]

The Gambia Hepatitis Study Group[2]

ABSTRACT

The Gambia Hepatitis Intervention Study is a large-scale vaccination project in The Gambia, initiated in July 1986, in which the introduction of national hepatitis B (HBV) vaccination of young infants progressively over a 4-year period is proposed. During this time it is anticipated that about 60,000 infants will receive a course of HBV vaccine and a similar number will not receive the vaccine. All children in the study will receive the normal childhood vaccinations. Identification data for each child will be collected and stored with information on their vaccination records. A national surveillance system will be set up to detect new cases of hepatocellular cancer and other chronic liver diseases over a period of 30 to 40 years. An attempt will be made to trace each case, of relevant age, to determine if they are included in the HBV vaccination study. In this way, the efficacy of HBV vaccine in the prevention of HCC and chronic liver diseases will be evaluated. Details of the study design are discussed.

INTRODUCTION

Chronic liver diseases and HCC[3] are major health problems

infection the HBsAg persistent carrier state is a major risk factor for HCC as well as for a high proportion of cases of chronic liver diseases.

The development of safe and effective subunit vaccines against HBV offers the potential for preventing a high incident cancer and for reducing the significant morbidity and mortality attendant on the other chronic sequelae of HBV infection.

In this paper we outline the design of a long-term study which has started recently in The Gambia to evaluate the impact of HBV vaccination on the incidence of HCC and other liver diseases.

NEED FOR A CONTROLLED VACCINE TRIAL

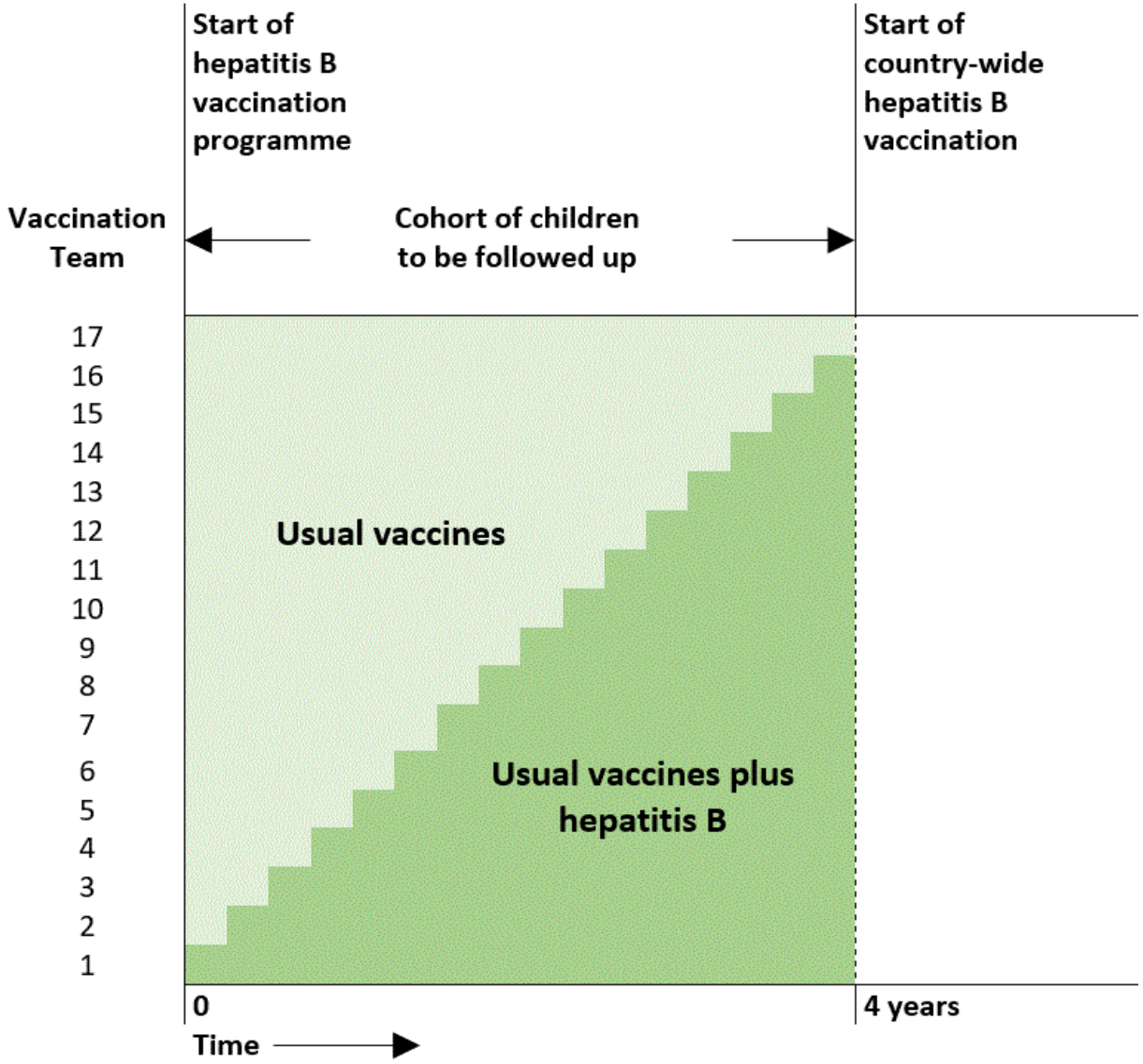
A number of trials have been conducted to assess the protective effect of the currently available plasma-derived HBV vaccines against HBV infections. These trials, in selected high-risk groups (*e.g.*, homosexuals, hospital personnel), have shown that

[CANCER RESEARCH 47, 5782–5787, November 1, 1987]

The Gambia Hepatitis Intervention Study

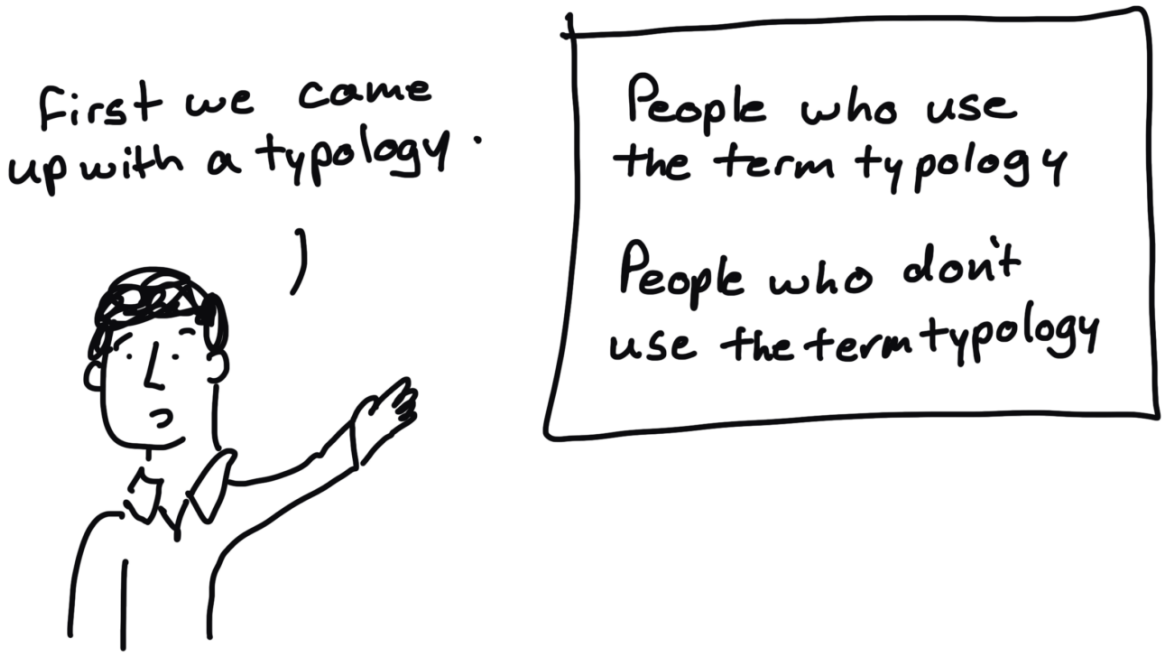
The Gambia Hepatitis Study Group[2]

17 regional vaccination teams randomised to different schedules for rolling out hep B vaccine for newborn infants, in a stepped wedge



A typology for stepped wedge trial designs

A typology for stepped wedge trial designs



freshspectrum
steppedwedgehog.blog

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Journal of Clinical Epidemiology 137 (2021) 159–162

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Key concepts in clinical epidemiology: Stepped wedge trials

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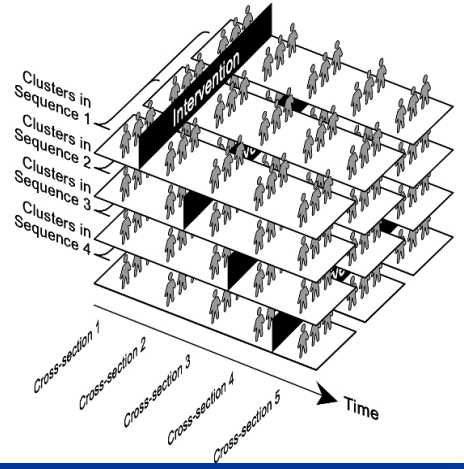
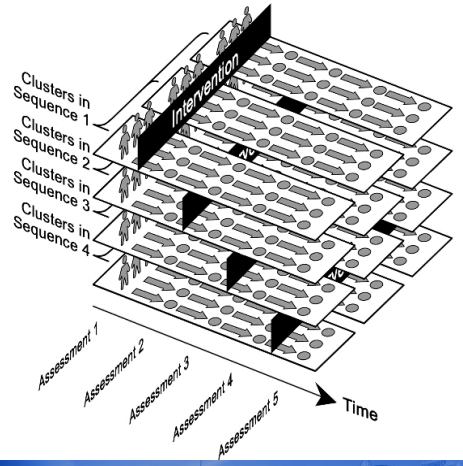
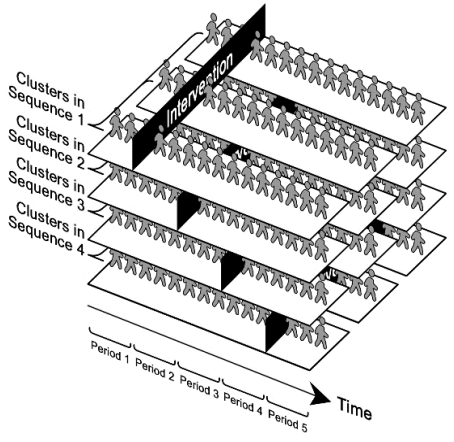
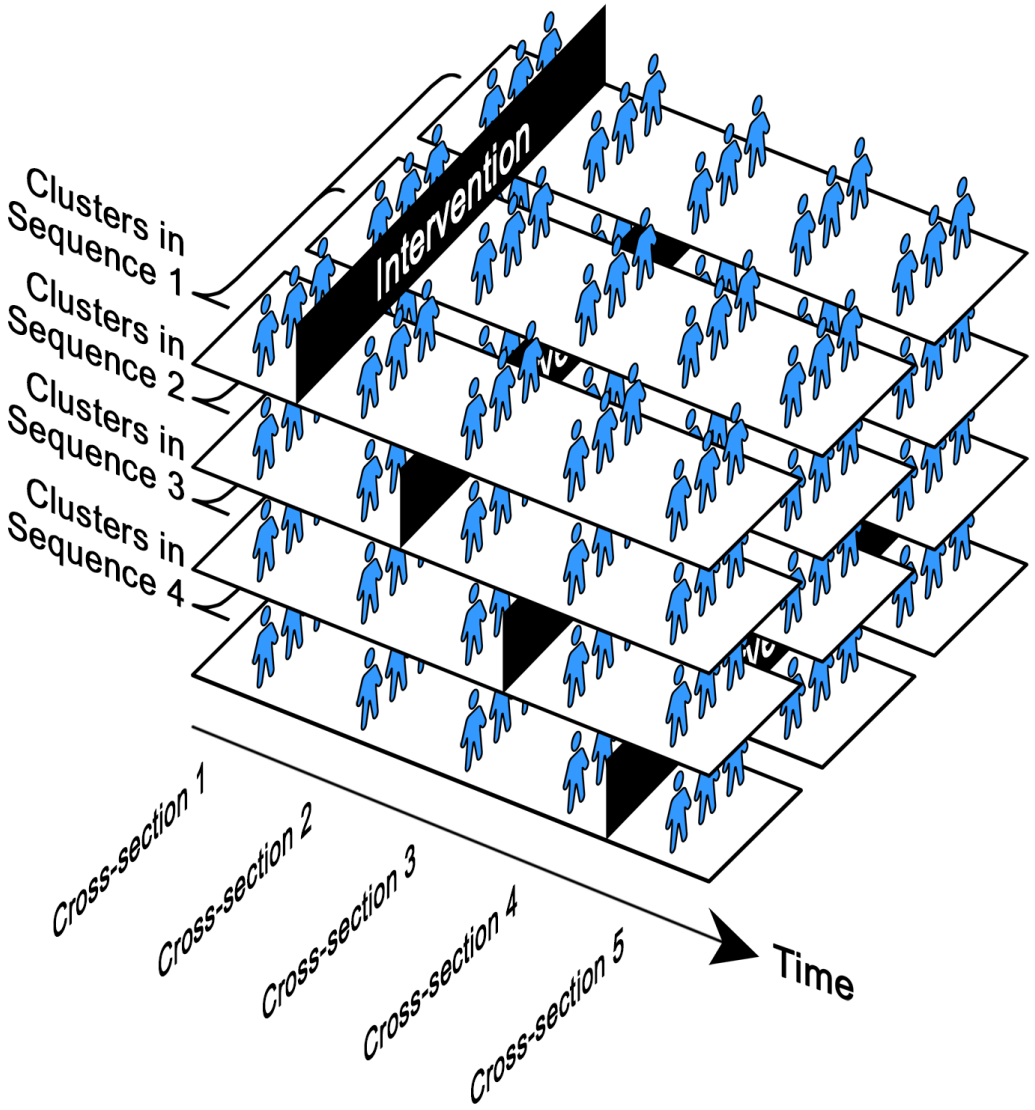
Received 16 March 2021; Received in revised form 10 April 2021; Accepted 13 April 2021; Available online 20 April 2021

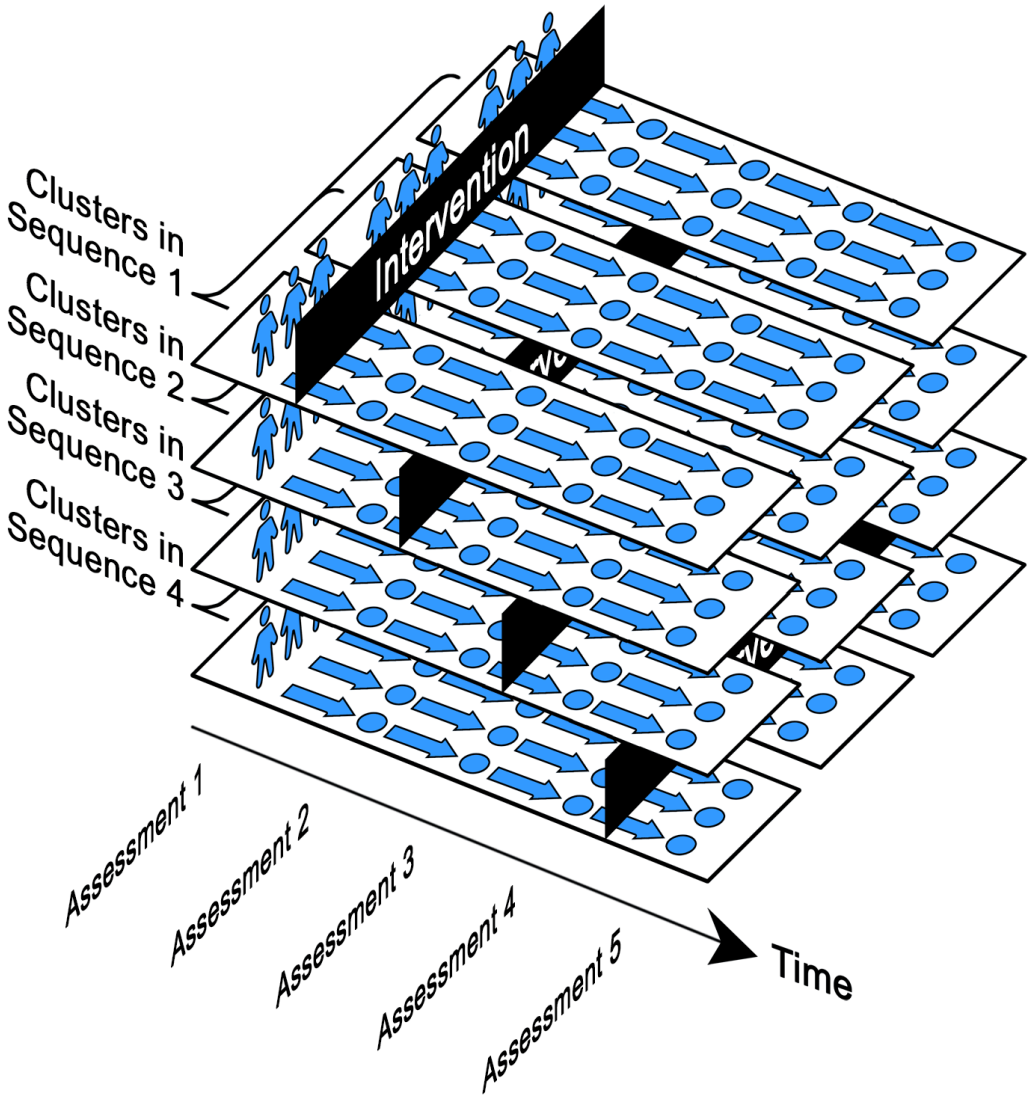




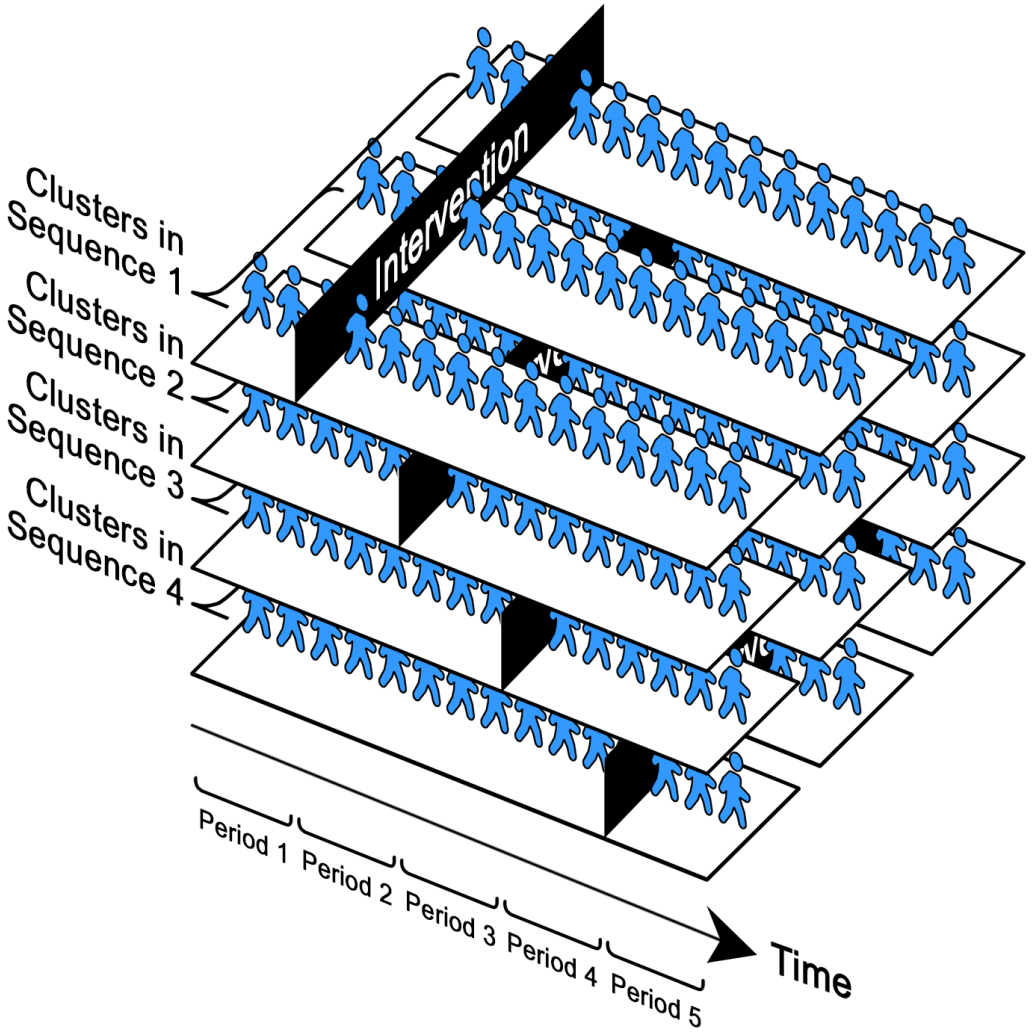




Repeated cross-section



Closed cohort



Continuous recruitment

New ways of thinking

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Journal of Clinical Epidemiology 116 (2019) 161–166

Journal of Clinical Epidemiology

COMMENTARY

Stepped wedge trials with continuous recruitment require new ways of thinking

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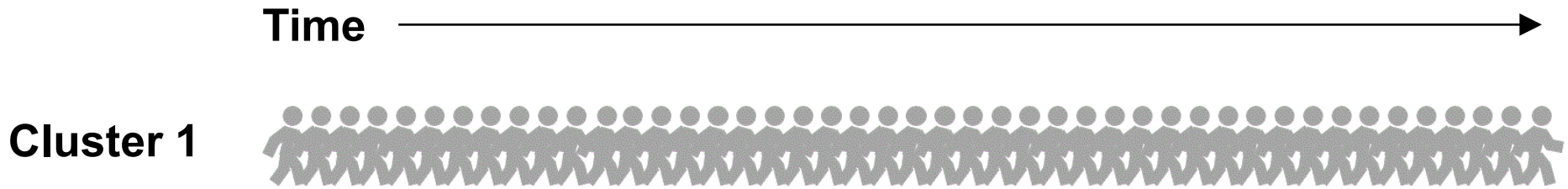
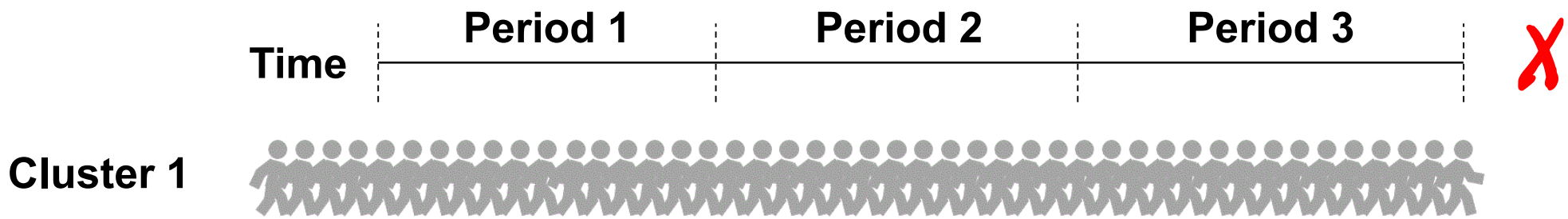
Accepted 29 May 2019; Published online 11 June 2019

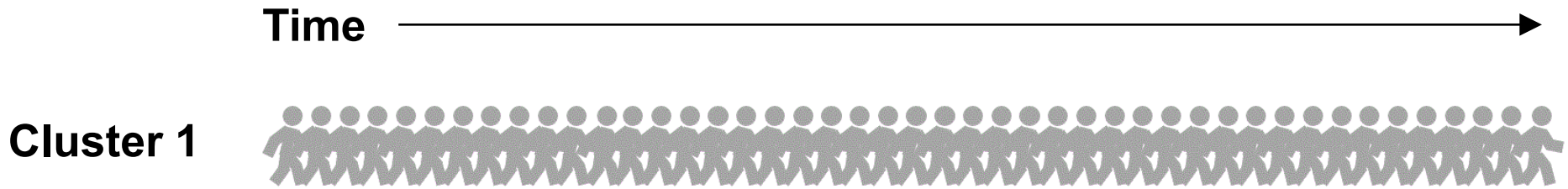
Continuous recruitment in a cluster



Continuous recruitment in a cluster



Continuous recruitment in a cluster



New ways of thinking

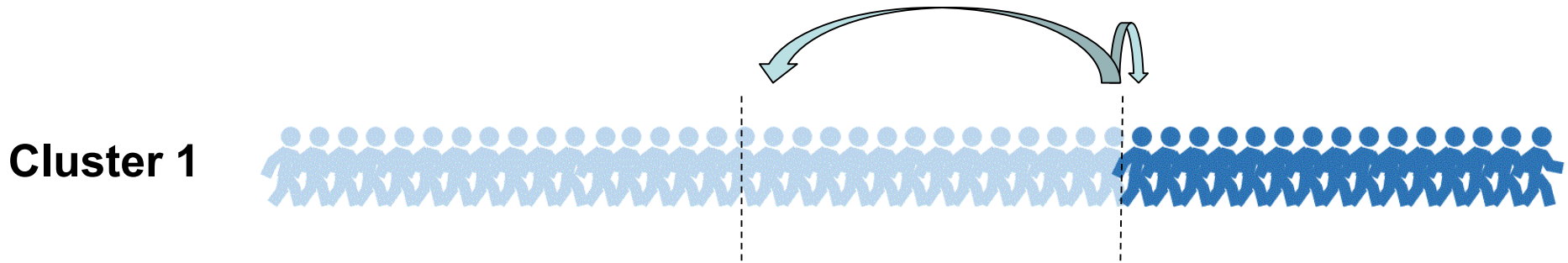
1. Crossing over to the intervention

Cluster 1

Recruitment under control condition

Recruitment under intervention condition

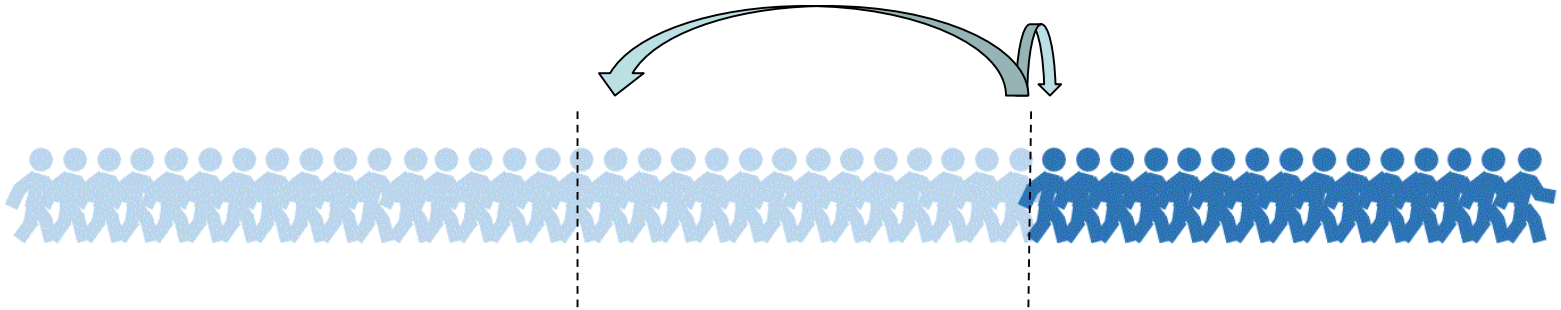
2. Modelling the cluster correlation



Longitudinal cluster randomised trials sometimes assume the intracluster correlation is exchangeable within “periods” of time.

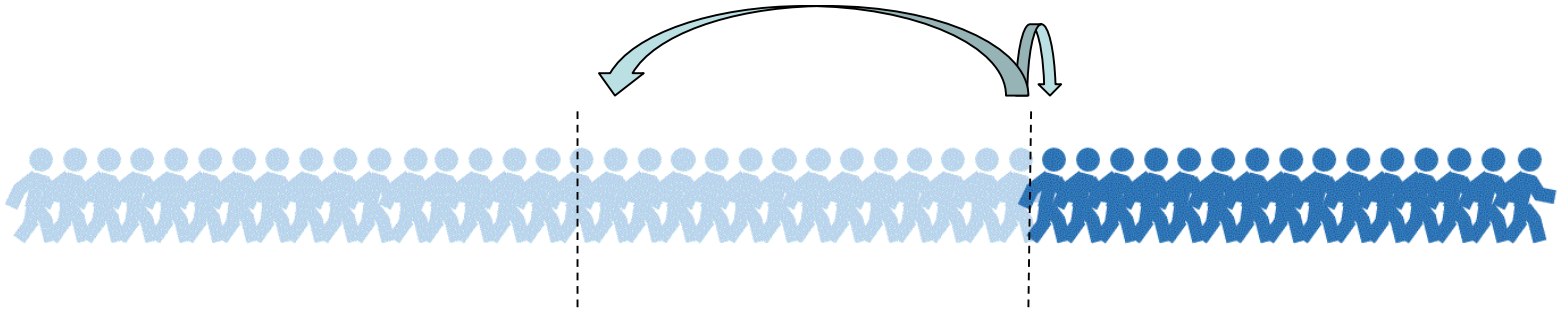
But when recruitment is continuous, which outcomes will be more closely correlated?

2. Modelling the cluster correlation



Makes more sense to assume the ICC decays with increasing separation in time

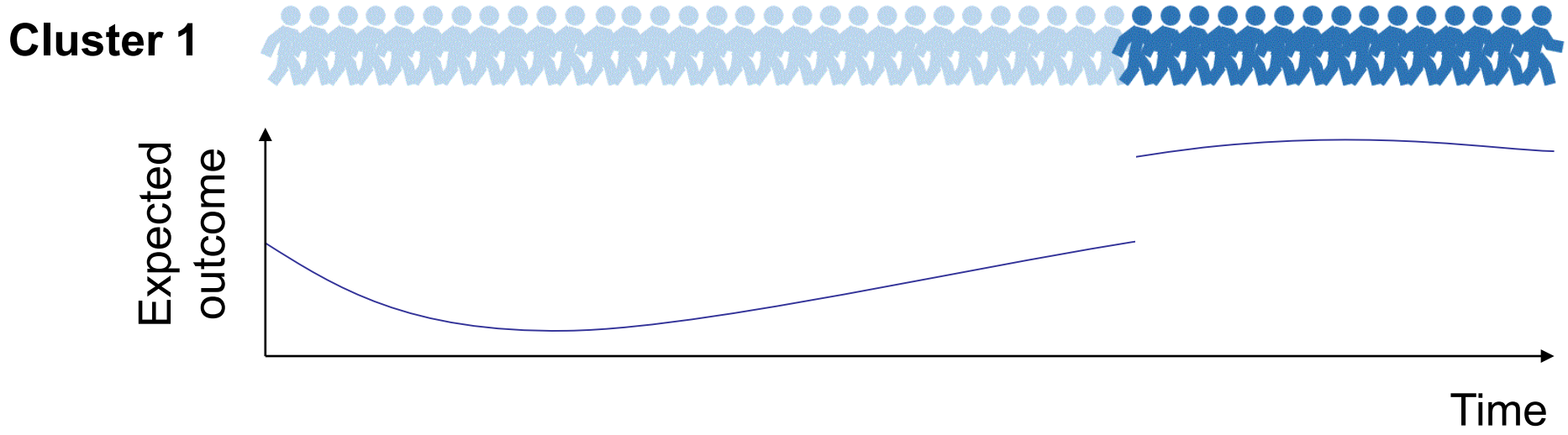
2. Modelling the cluster correlation



Makes more sense to assume the ICC decays with increasing separation in time

ICC = $\rho\tau^{|t_2-t_1|}$, $t = 0$ at the start of the trial, and $t = 1$ at the end

3. Modelling the underlying effect of time



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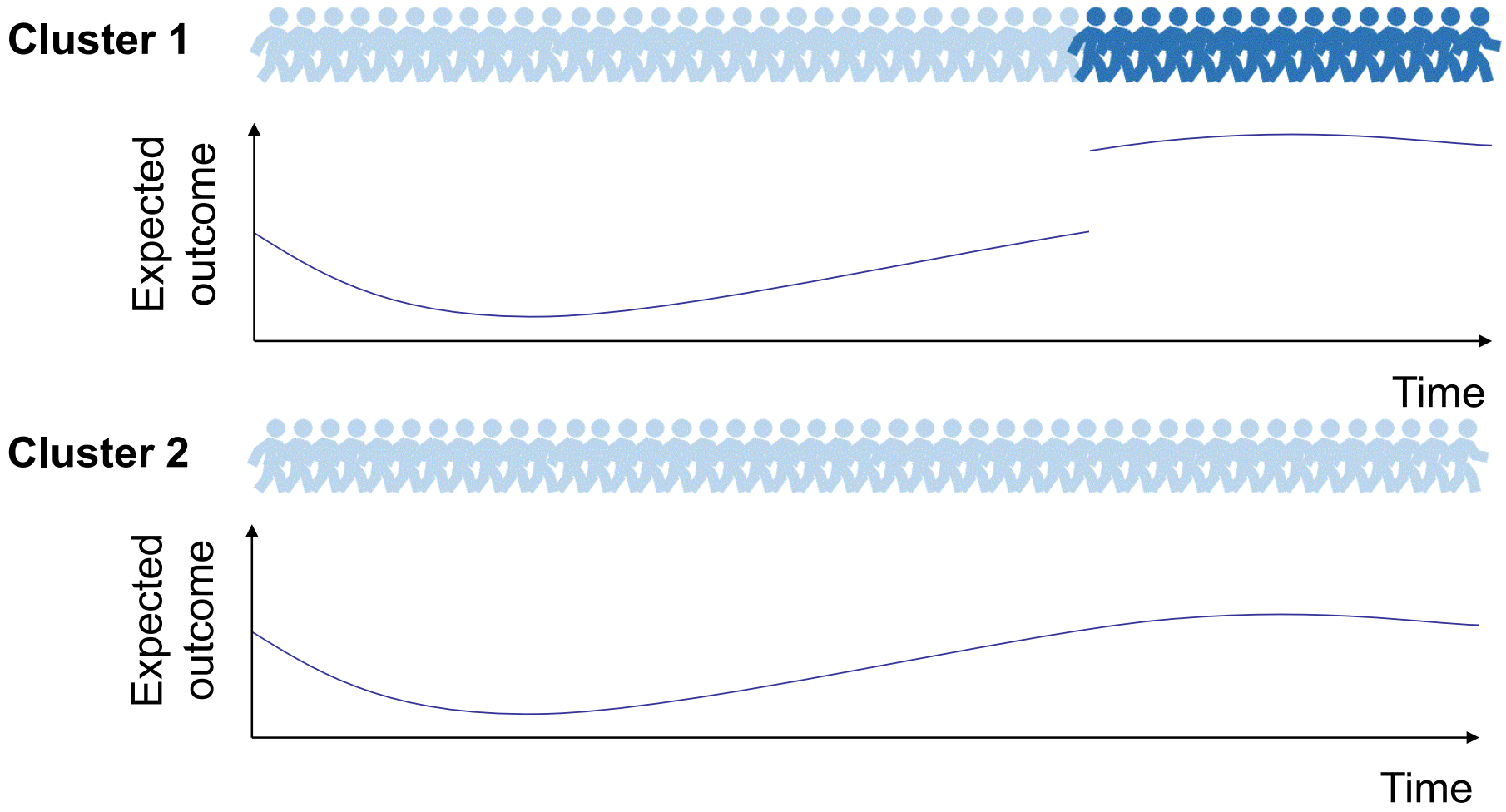
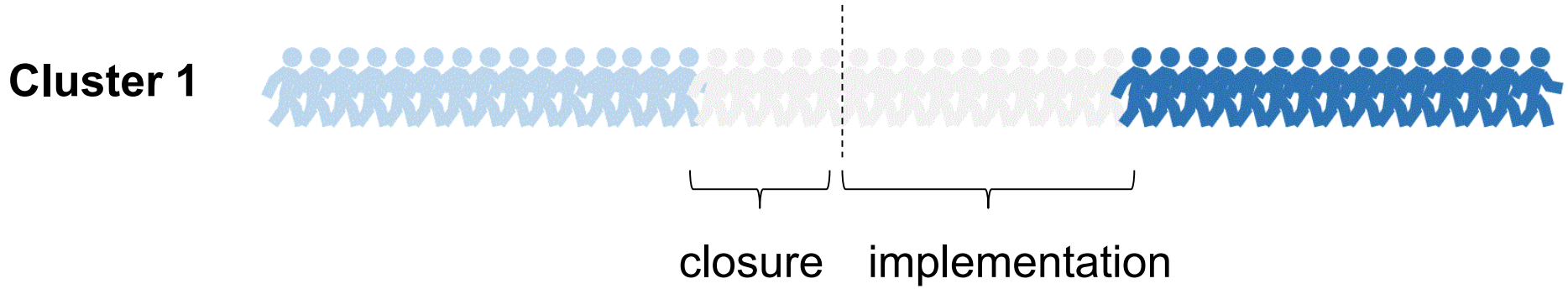


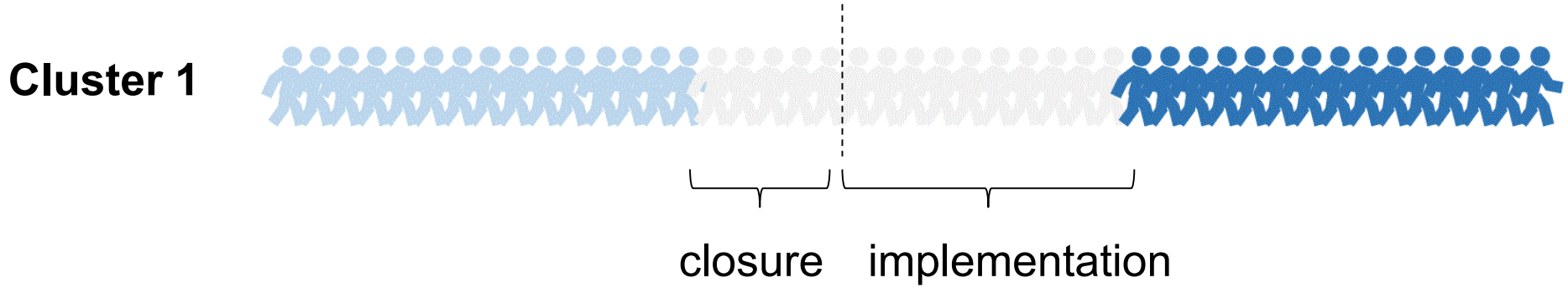
4. Allowing for a transition period

Cluster 1

4. Allowing for a transition period



4. Allowing for a transition period



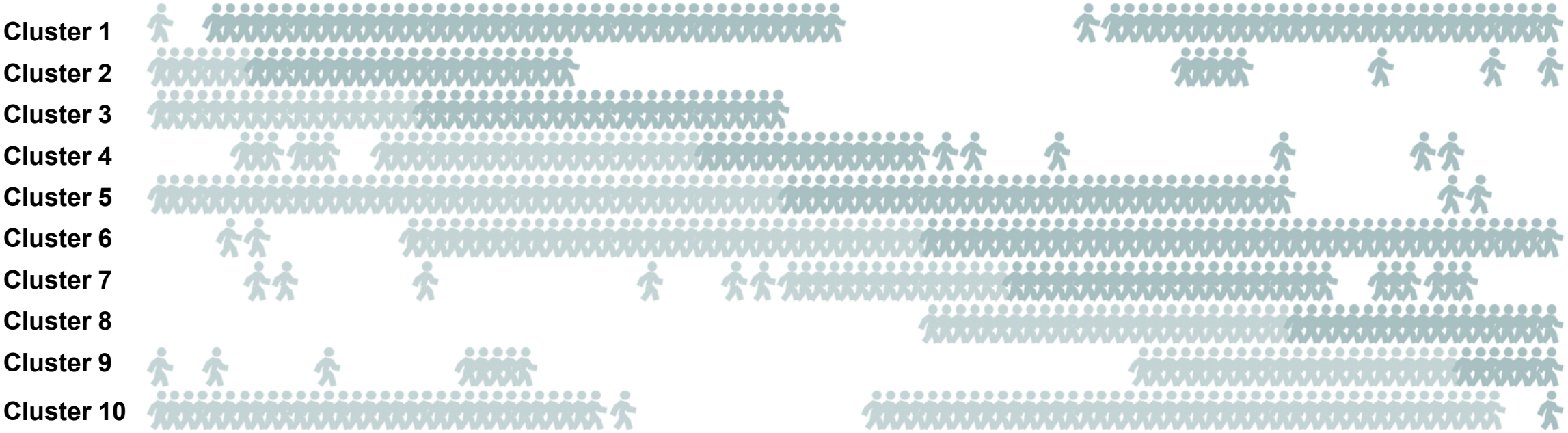
The closure period should be long enough for the last participant recruited under the control condition to have left the cluster or to have been assessed

5. Incomplete designs

Cluster 1

You may not want to recruit every available participant
(*e.g.* if there is a financial or ethical cost per participant)

5. Incomplete designs



Some methods

Statistical model

Participant i in cluster k is recruited at time t_{ik}

Cluster k crosses from control to intervention at time t_k^*

Model for continuous outcome Y_{ik} is

$$Y_{ik} = T(t_{ik}) + \delta . H(t_{ik} - t_k^*) + e_{ik}$$

where $T(t)$ is the effect of time common to all clusters, $H(t)$ is the step function, and δ is the intervention effect

Generalised least squares estimation

Write outcomes Y_{ik} as column vector $\mathbf{Y}$

$$\mathbf{Y} = \mathbf{Z\theta} + \mathbf{e}, \quad \mathbf{e} \sim N(\mathbf{0}, \mathbf{V})$$

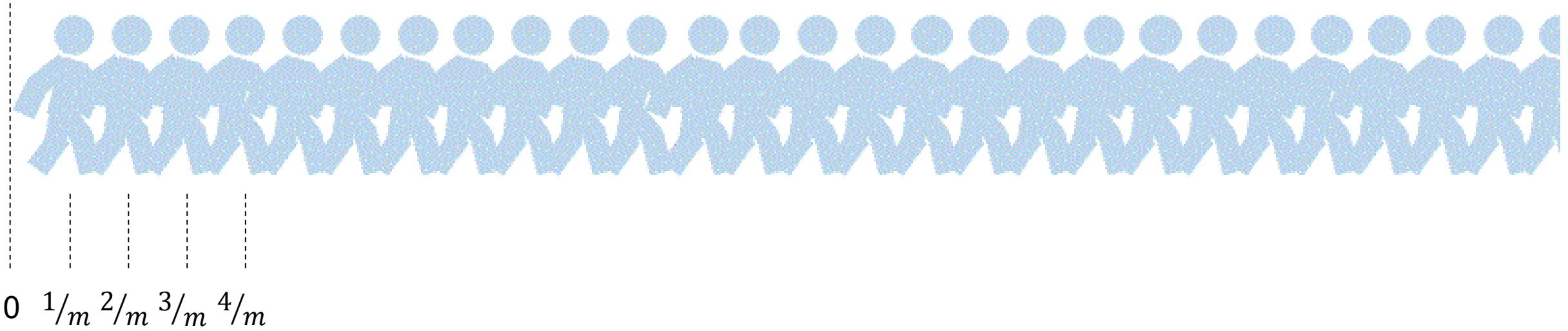
where $\boldsymbol{\theta}$ is a vector of parameters, including δ and the parameterisation of the time effect $T(t)$

Then the variance of the GLS estimator for $\boldsymbol{\theta}$ is

$$\mathrm{Var}(\hat{\boldsymbol{\theta}}) = (\mathbf{Z}'\mathbf{V}^{-1}\mathbf{Z})^{-1}$$

Simplification/regularisation of recruitment times

Participant i in cluster k is recruited at time t_{ik}



Some design problems

- Cluster randomised trials with a prospective baseline

Article

CLINICAL TRIALS

Clinical Trials
2021, Vol. 18(2) 147–157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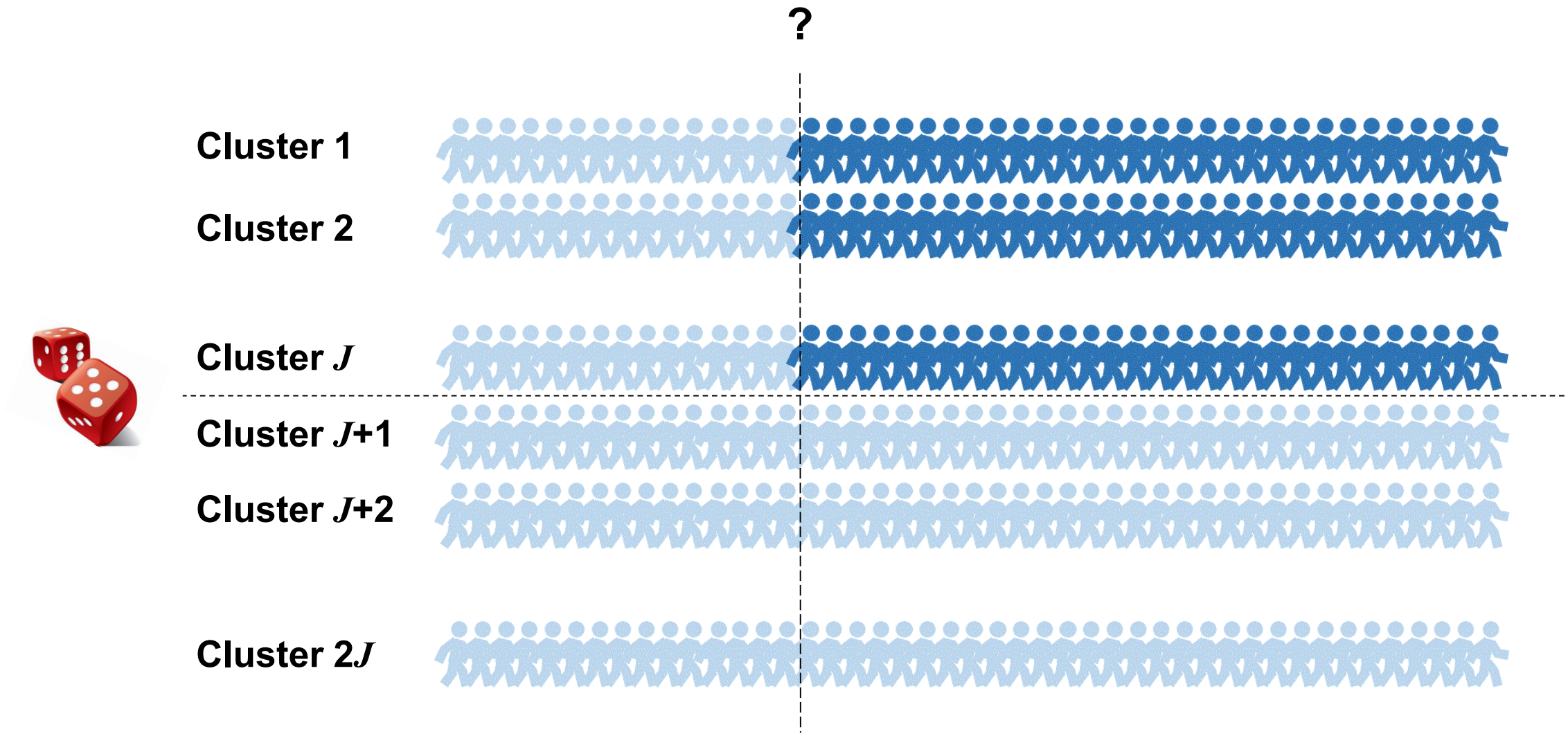
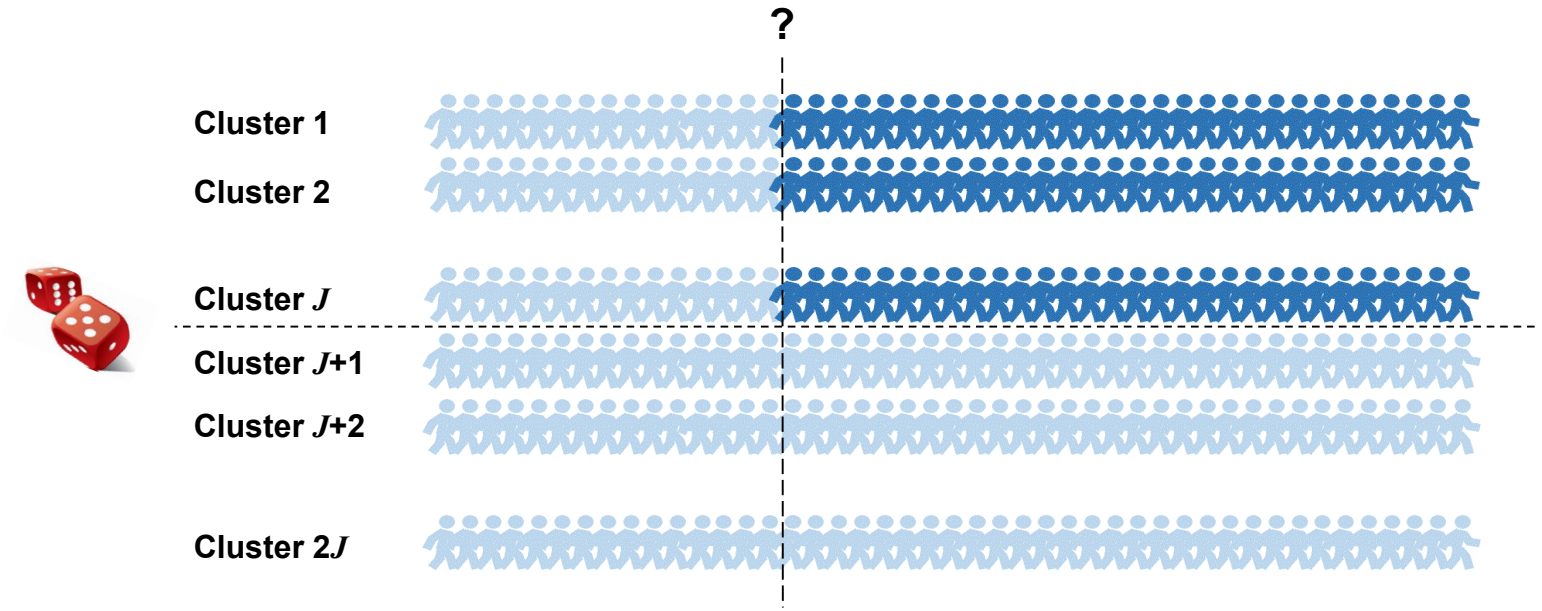
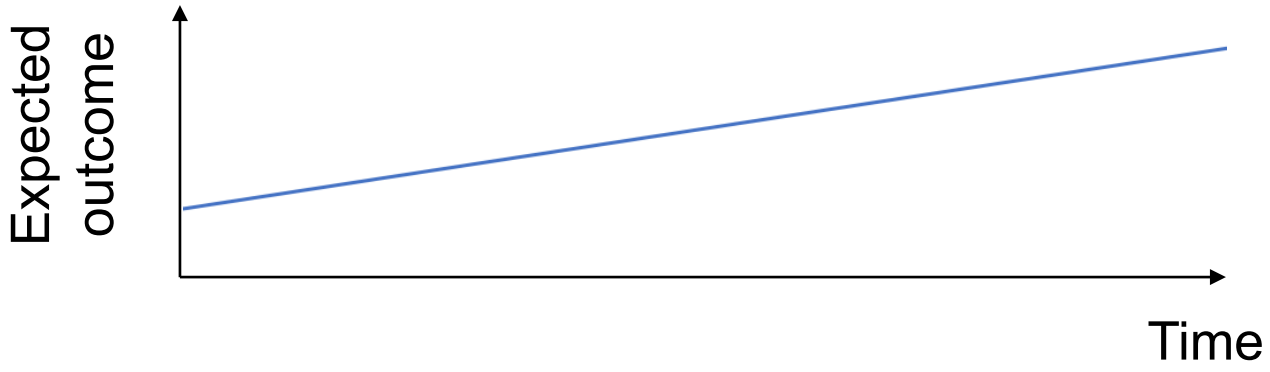
Optimal design of cluster randomised trials with continuous recruitment and prospective baseline period

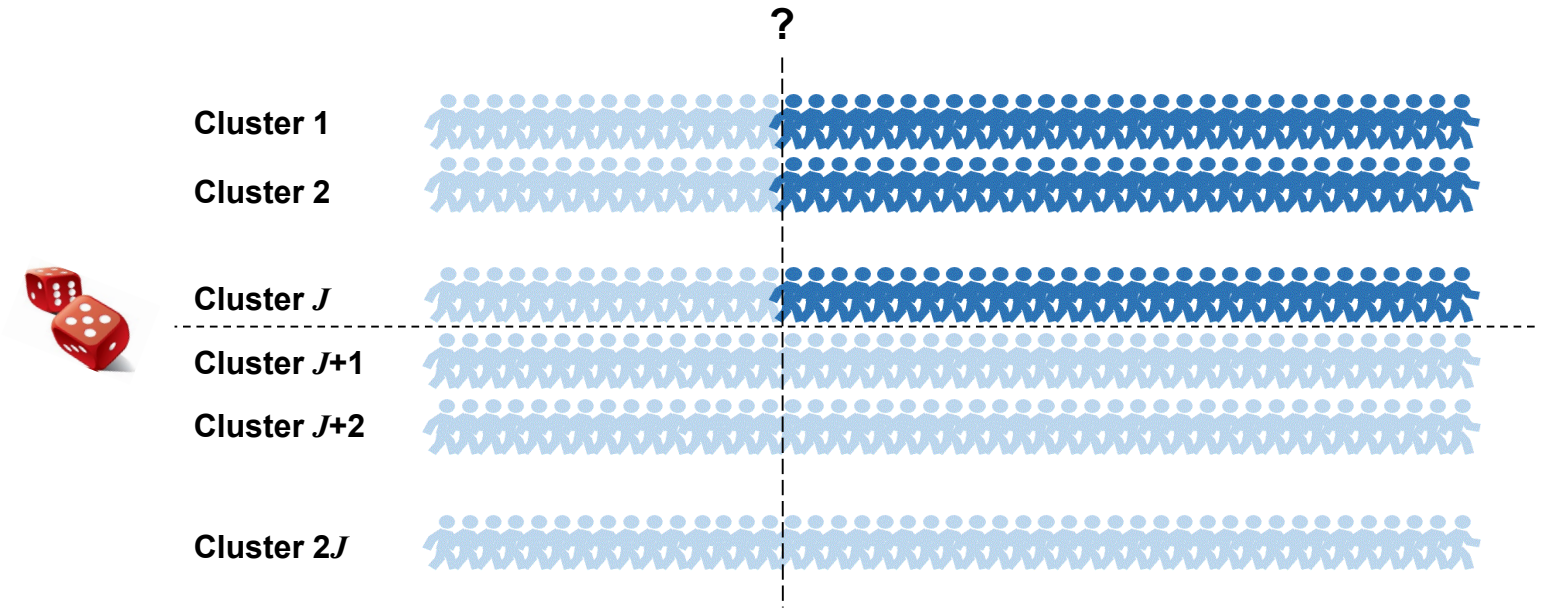
Richard Hooper[1] and **Andrew J Copas**[2]

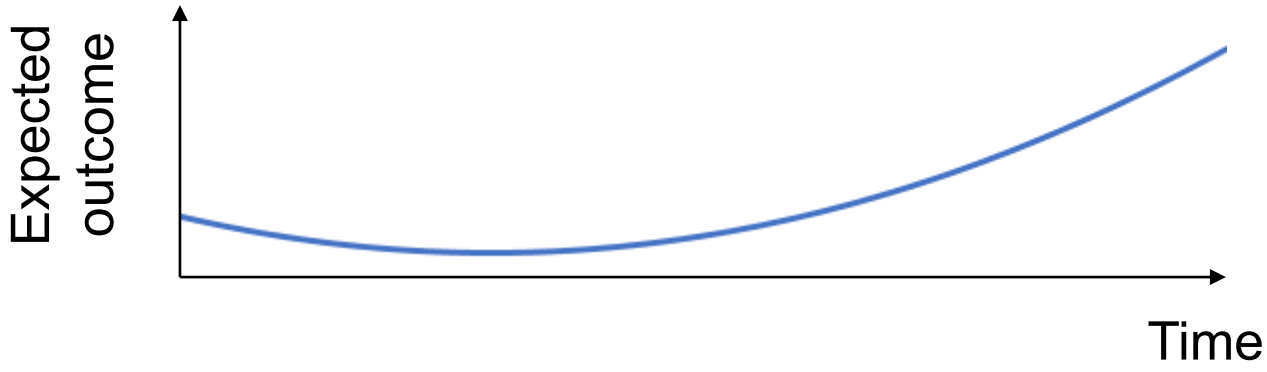

?
Cluster 1
Cluster 2
Cluster J
Cluster J+1
Cluster J+2
Cluster 2J



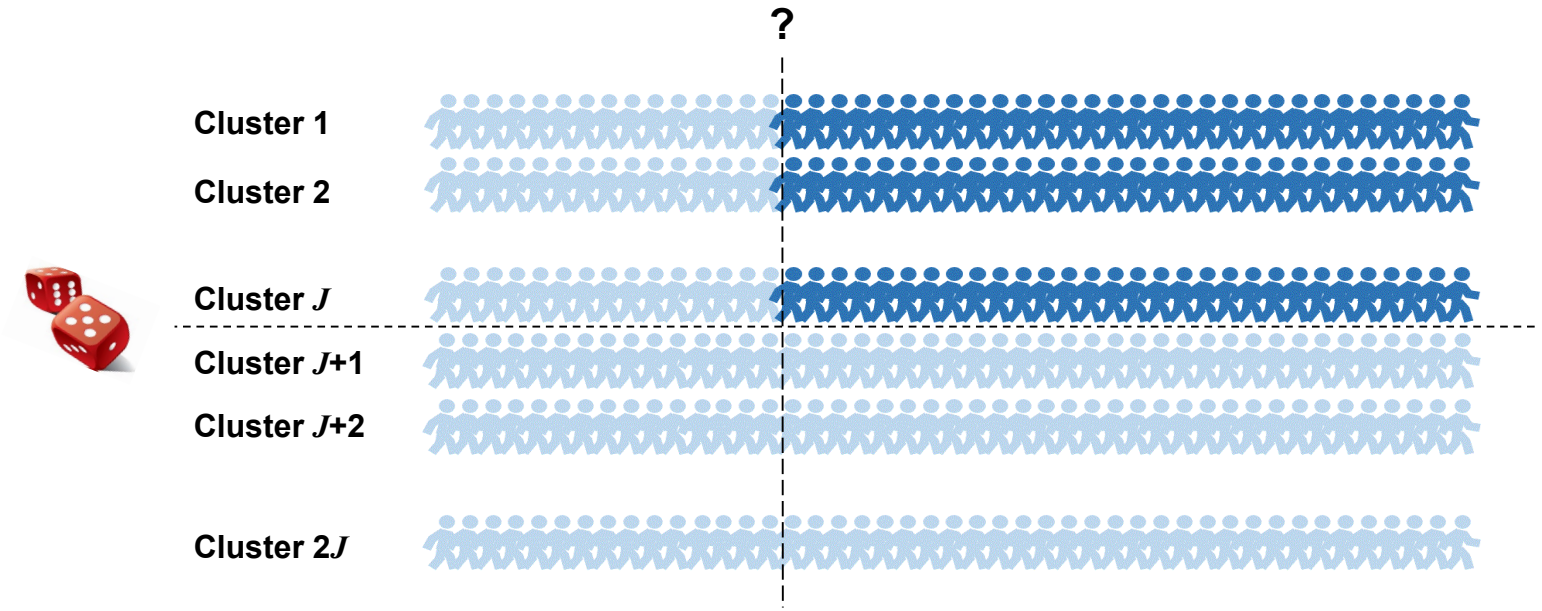


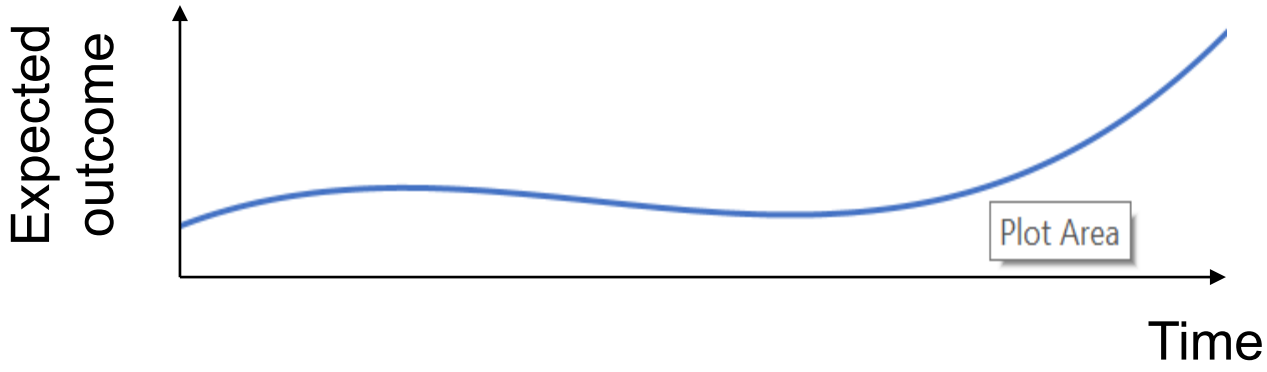
Linear effect of time



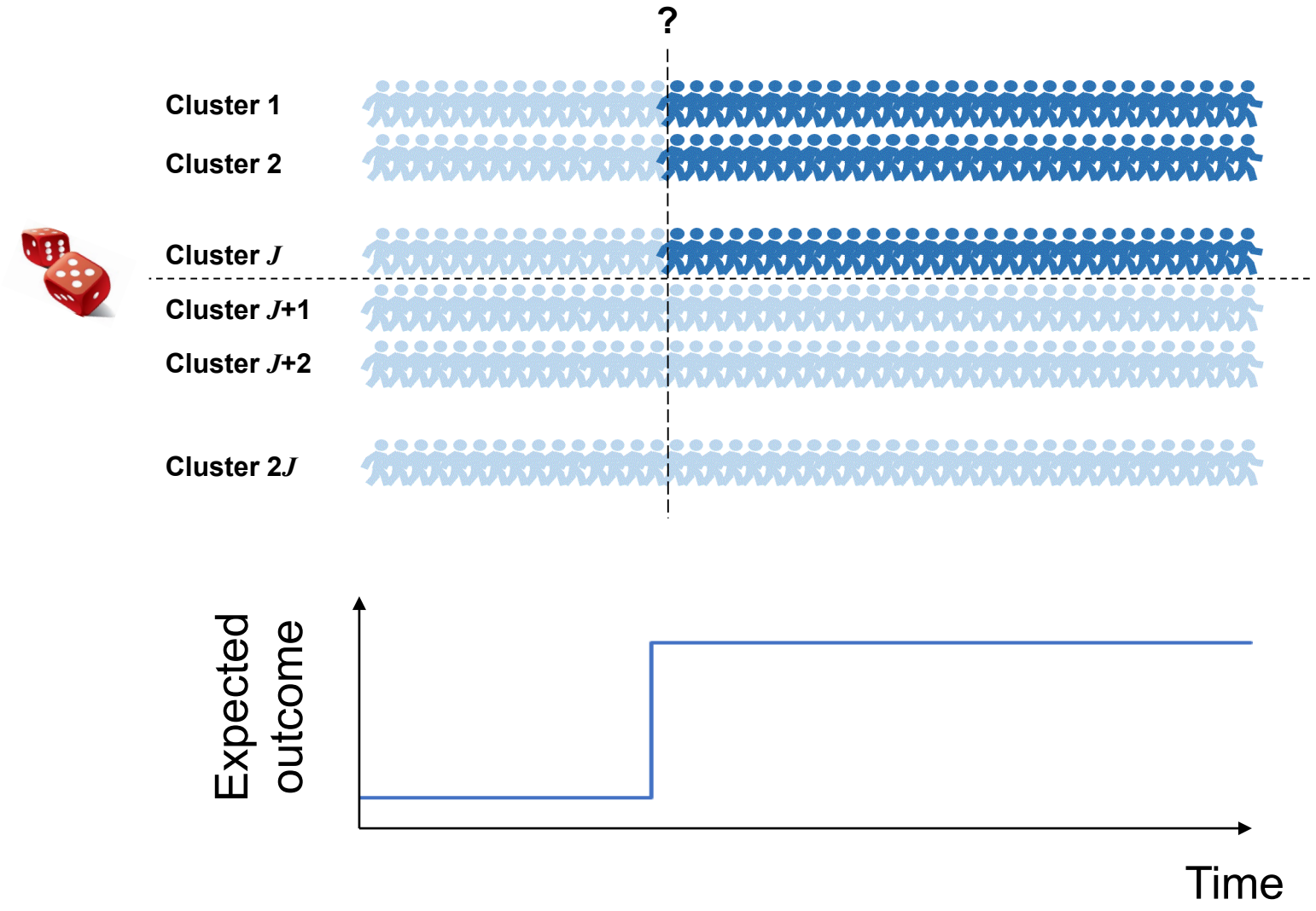


Quadratic effect of time





Cubic effect of time



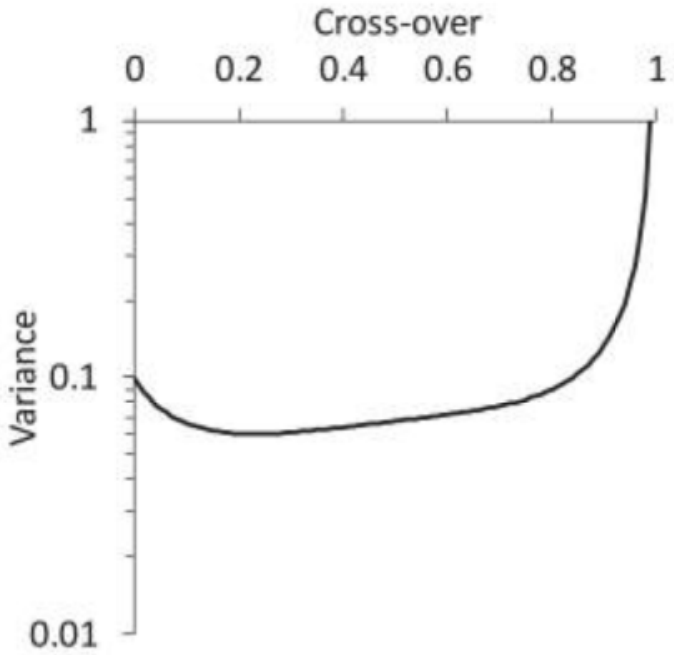
Discontinuous effect of time

Variance of treatment effect estimator

$m = 100$

$\rho = 0.05$

$\tau = 0.5$ linear



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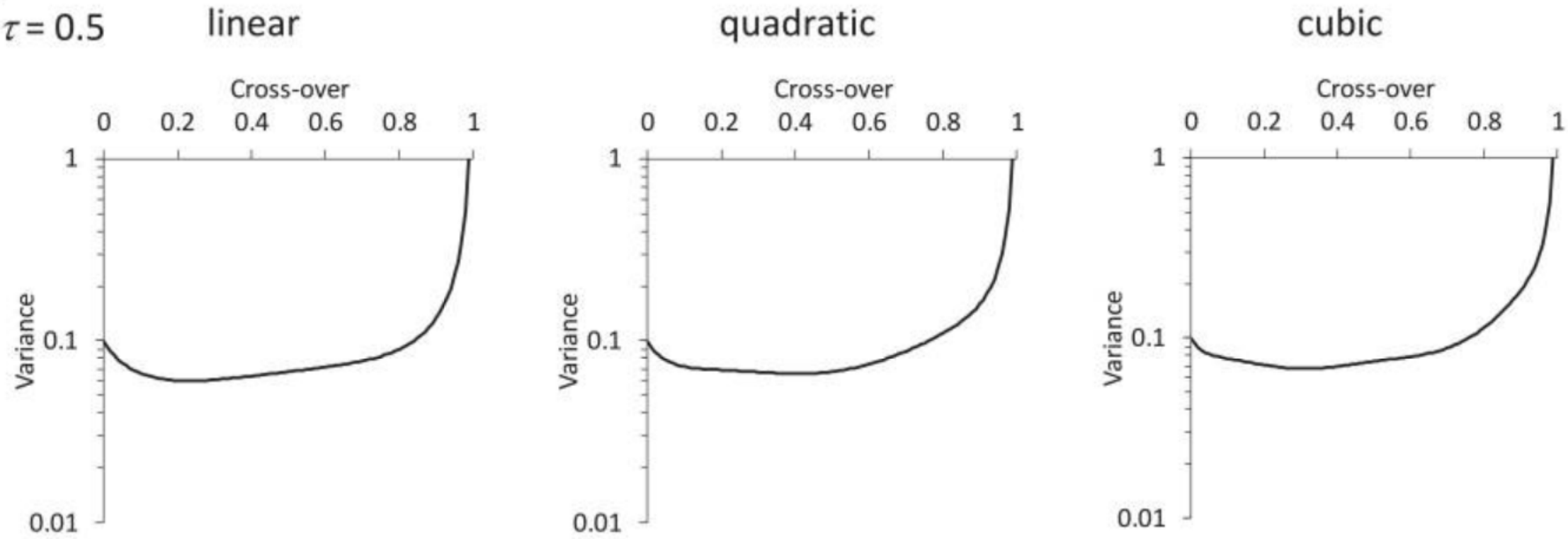
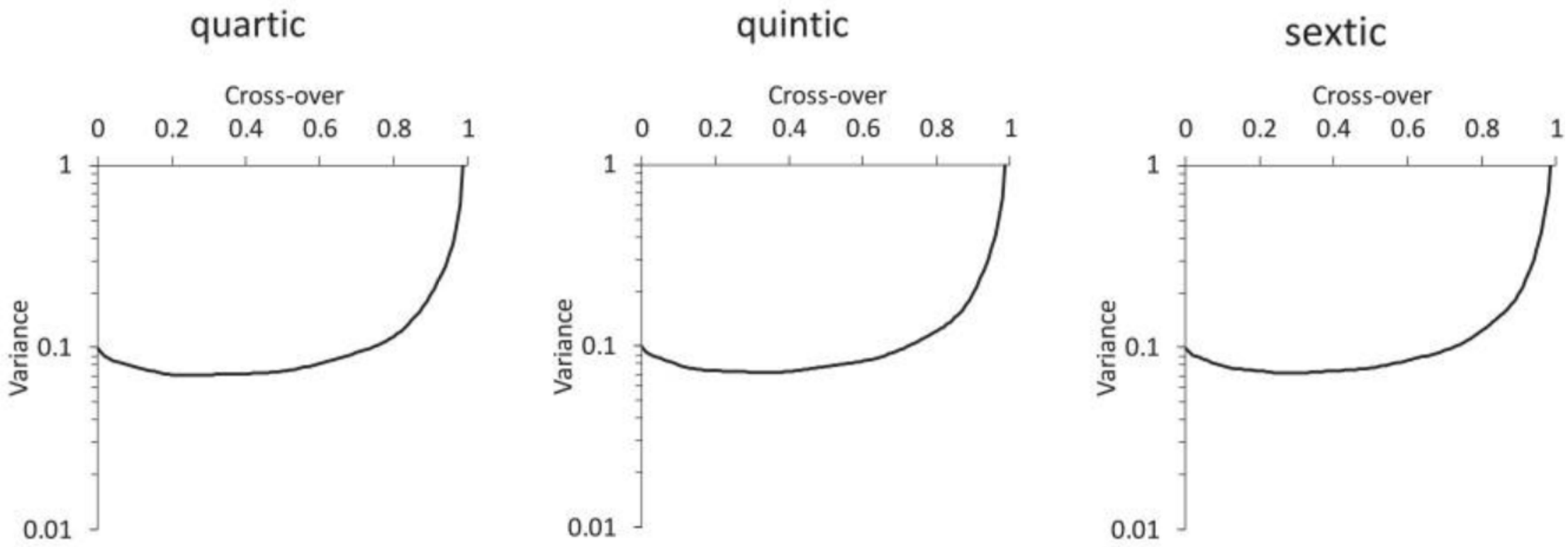
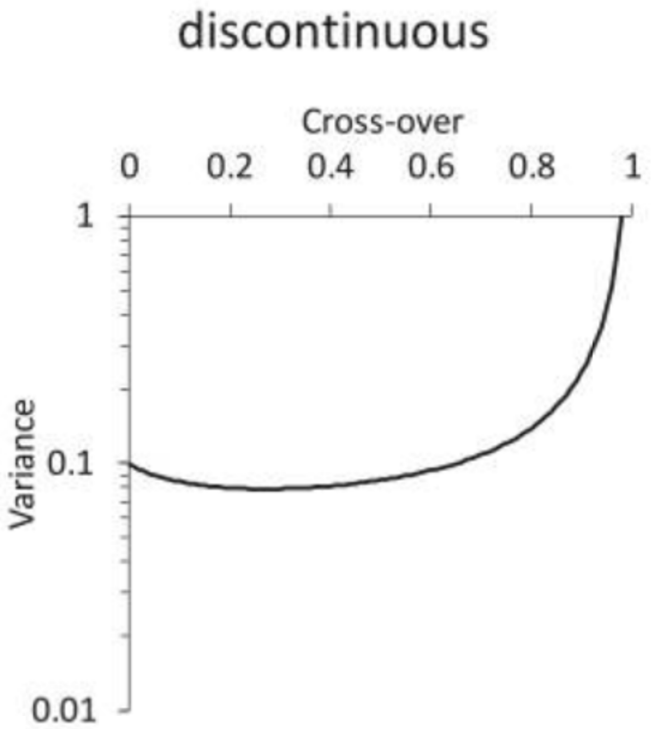


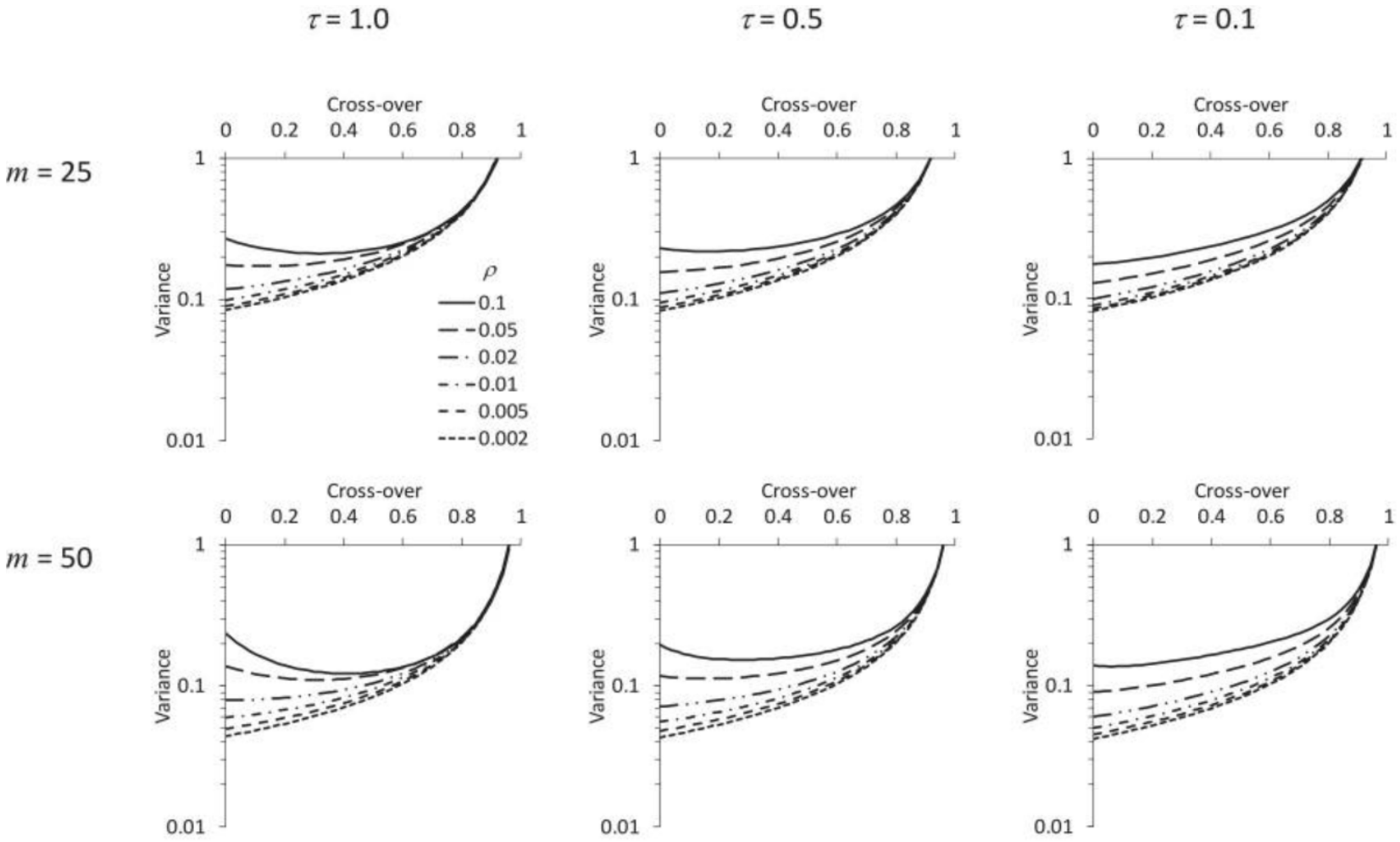
Variance of treatment effect estimator



Variance of treatment effect estimator



Variance of treatment effect estimator



Simple rule of thumb

You will not go far wrong by choosing between no baseline period, or a baseline period half the length of the recruitment period, whichever leads to the smaller variance

Simple rule of thumb

You will not go far wrong by choosing between no baseline period, or a baseline period half the length of the recruitment period, whichever leads to the smaller variance

A baseline period is not needed in the following situations:

$\tau = 1.0$: $m\rho \leq 1$

$\tau = 0.5$: $m\rho \leq 2$

$\tau = 0.1$: $m\rho \leq 5$

- Complete stepped wedge trials

Optimal stepped-wedge cluster randomised trial designs for non-uniform correlation structures

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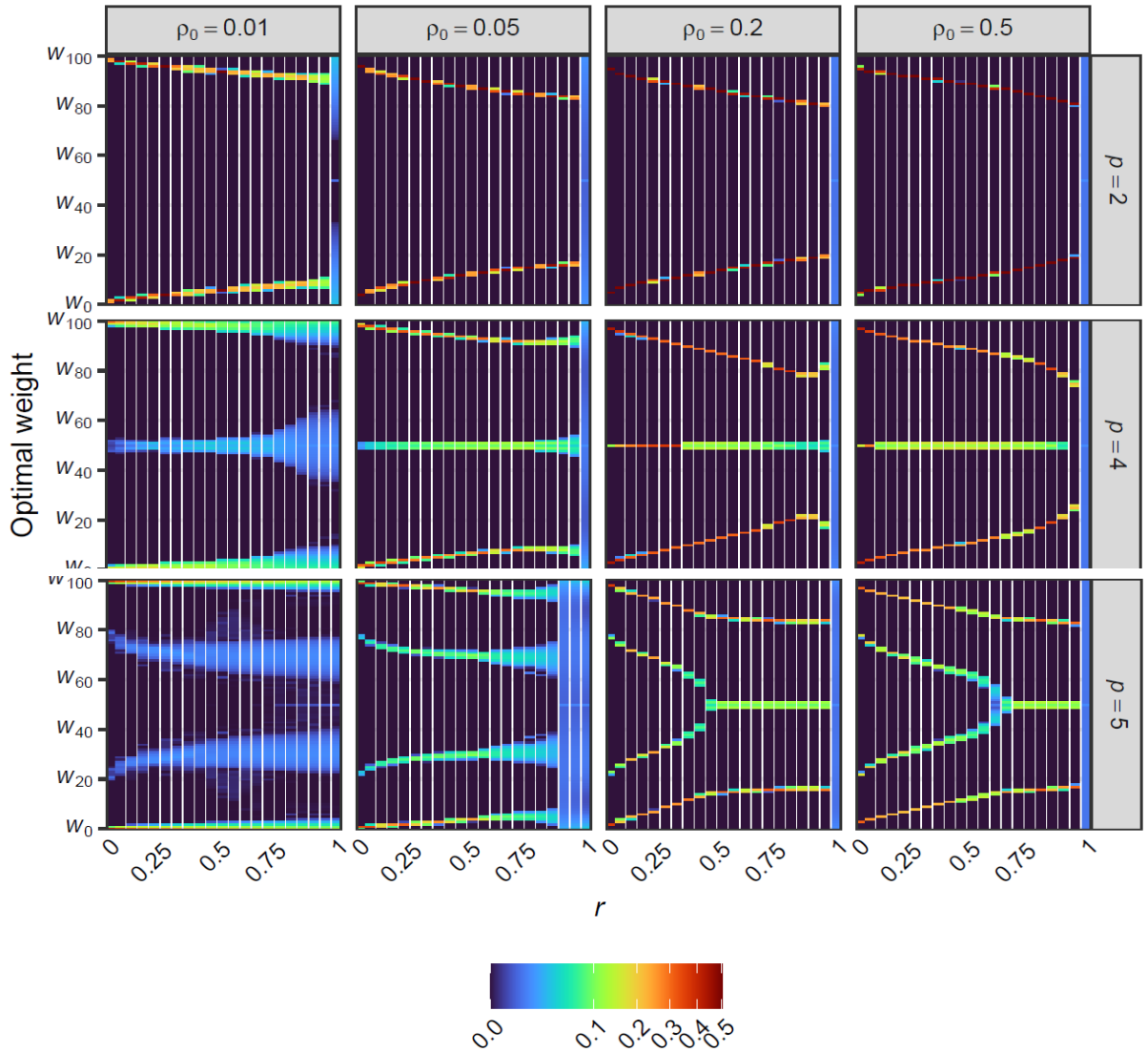
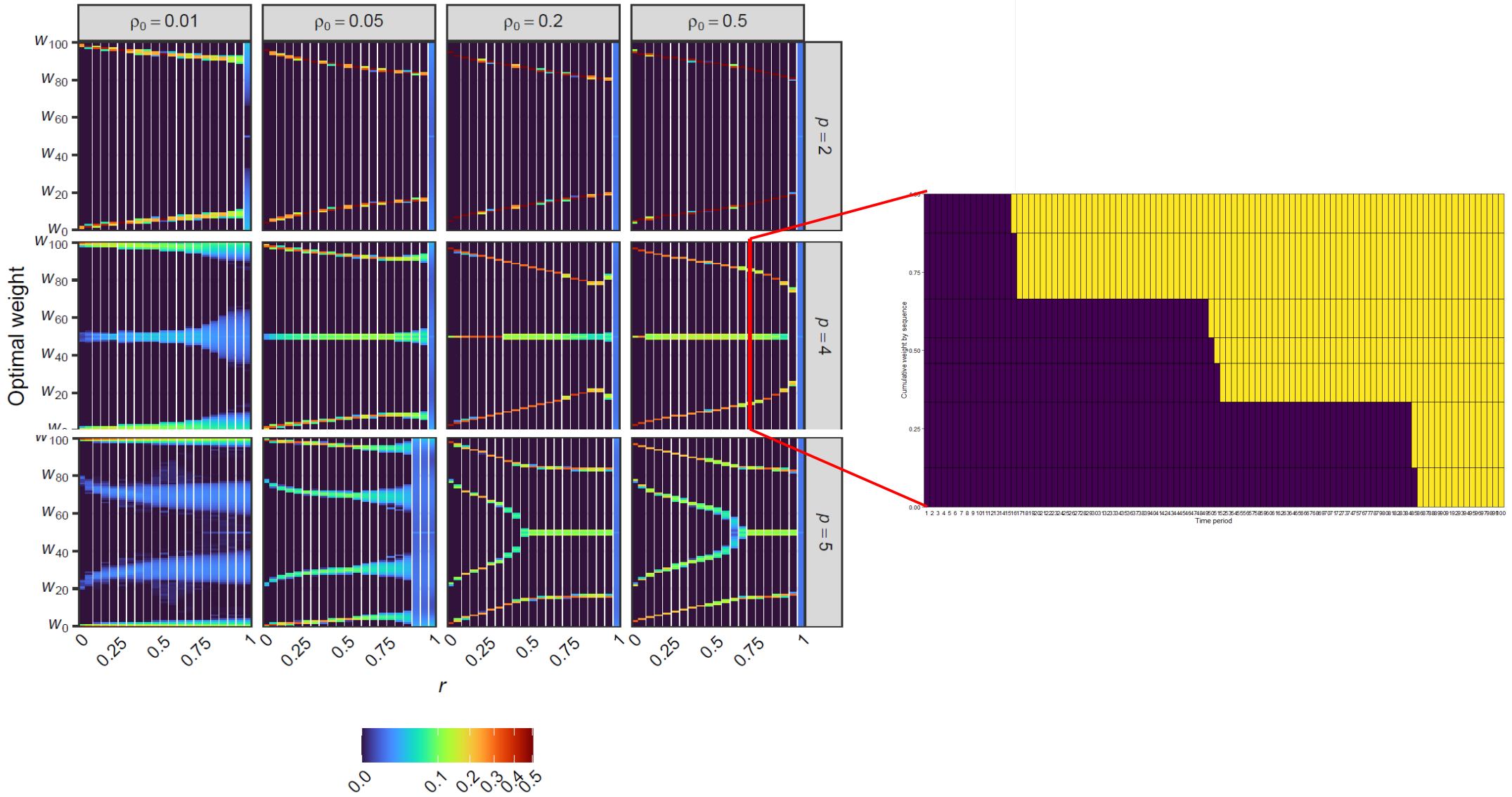
- Complete stepped wedge trials
  - $m = 100$
  - Regularised recruitment times $^{1}/_{100}, ^{2}/_{100}, ^{3}/_{100}, \cdots$
  - Number of clusters $\gg 100$
  - How should we weight the clusters over the 101 possible cross-over sequences?

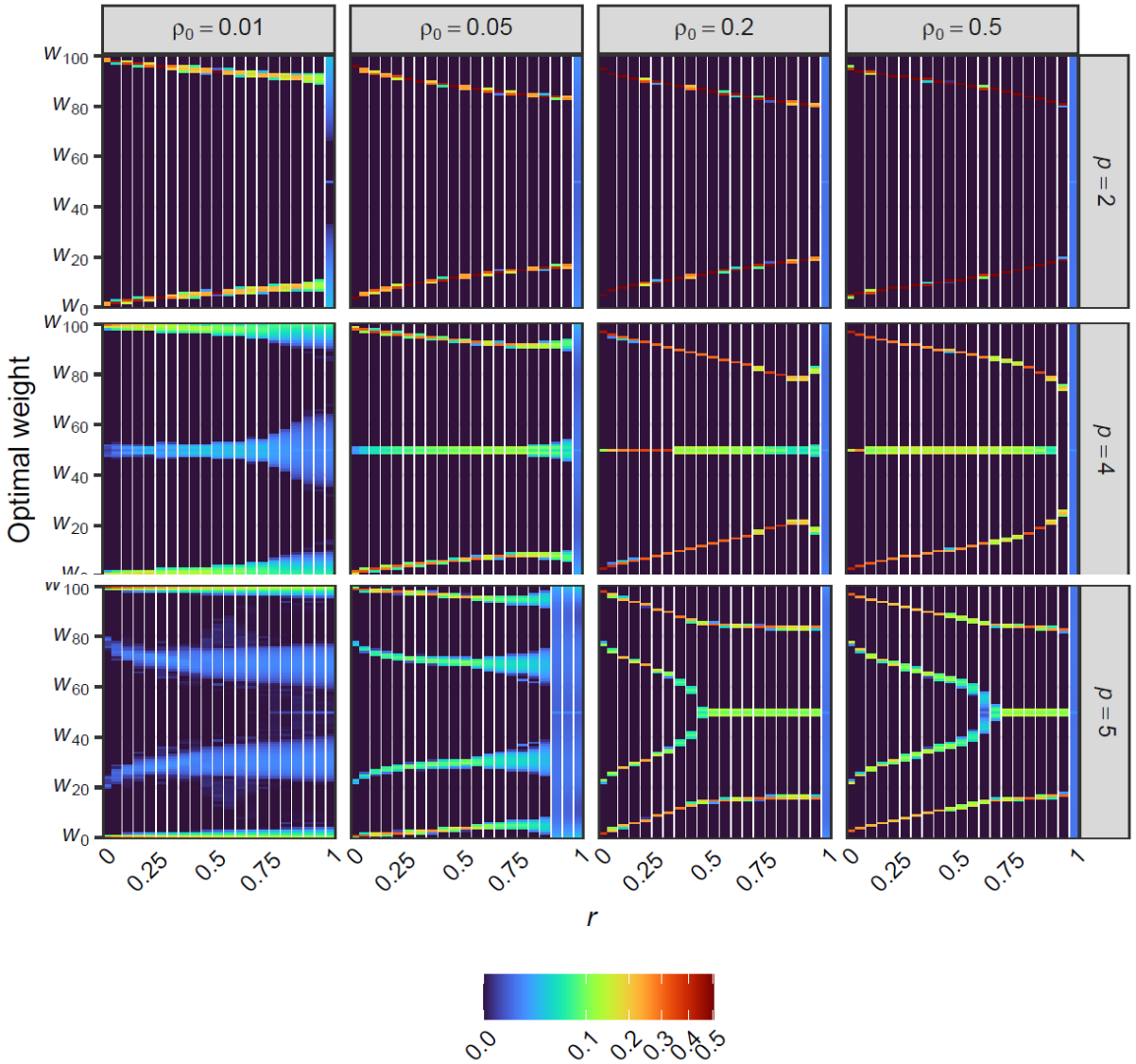


quadratic time effect

quartic time effect

quintic time effect


ρ0 = 0.01
ρ0 = 0.05
ρ0 = 0.2
ρ0 = 0.5
p = 2
p = 4
p = 5
Optimal weight
w100
w80
w60
w40
w20
w0
0
0.25
0.5
0.75
1
r
0.0
0.1
0.2
0.3
0.4
0.5
Cumulative weight by sequence
Time period



quadratic time effect

quartic time effect

quintic time effect

- Incomplete stepped wedge trials

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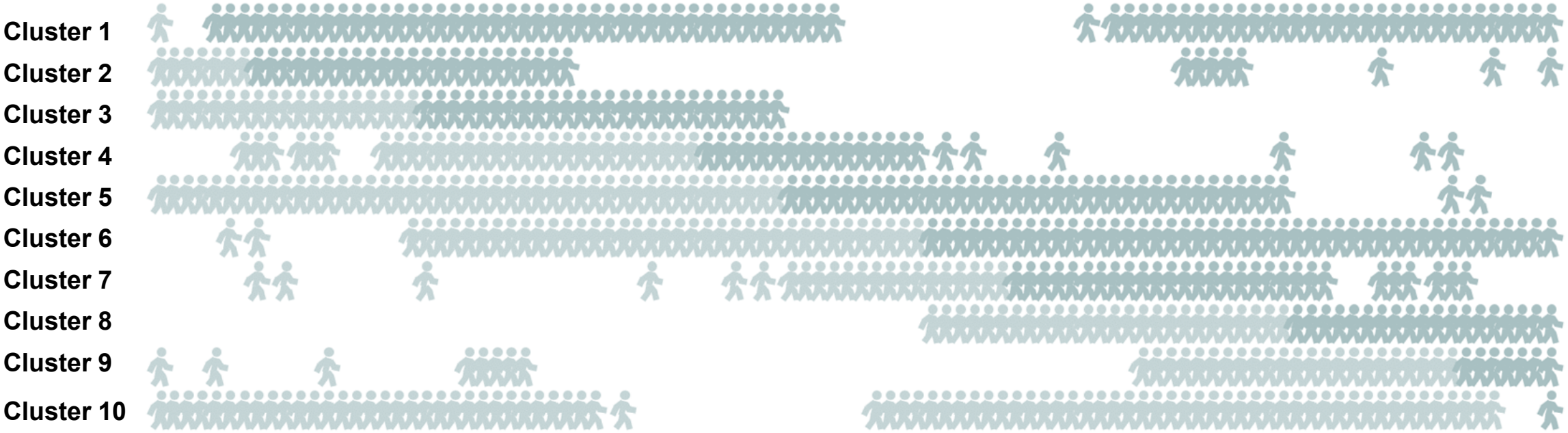
BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

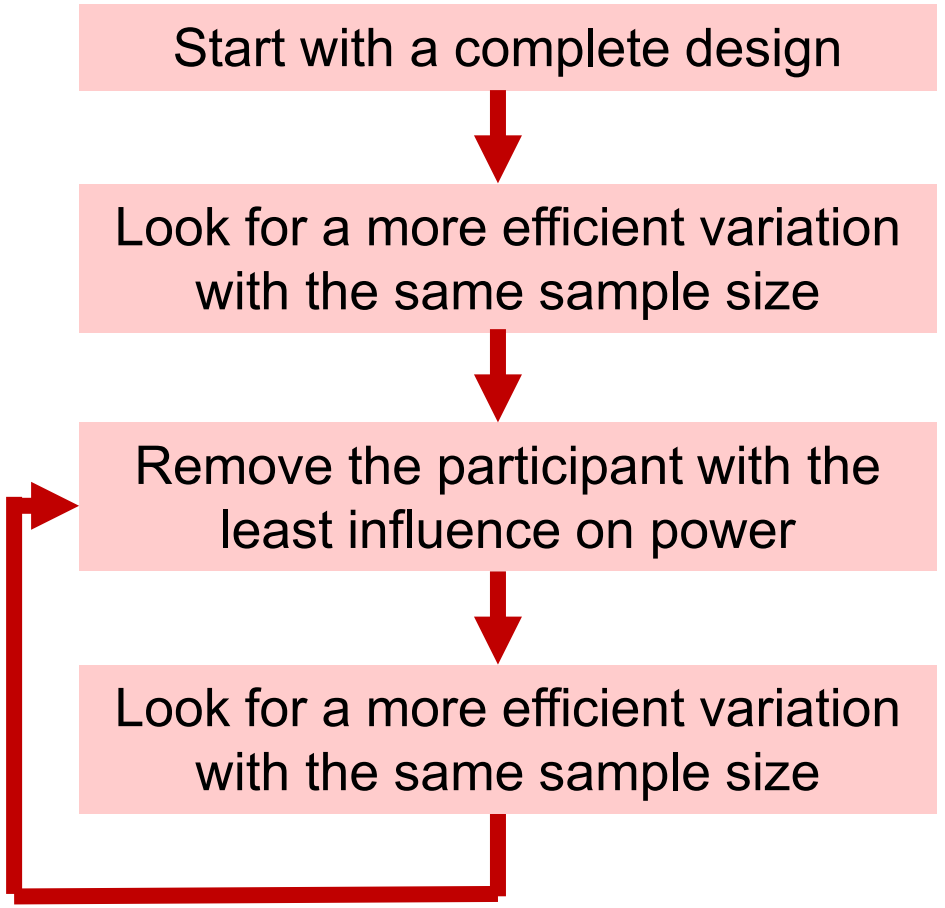
The hunt for efficient, incomplete designs for stepped wedge trials with continuous recruitment and continuous outcome measures

Richard Hooper[1,2*], Jessica Kasza[3] and Andrew Forbes[3]

- Incomplete stepped wedge trials



Search algorithm

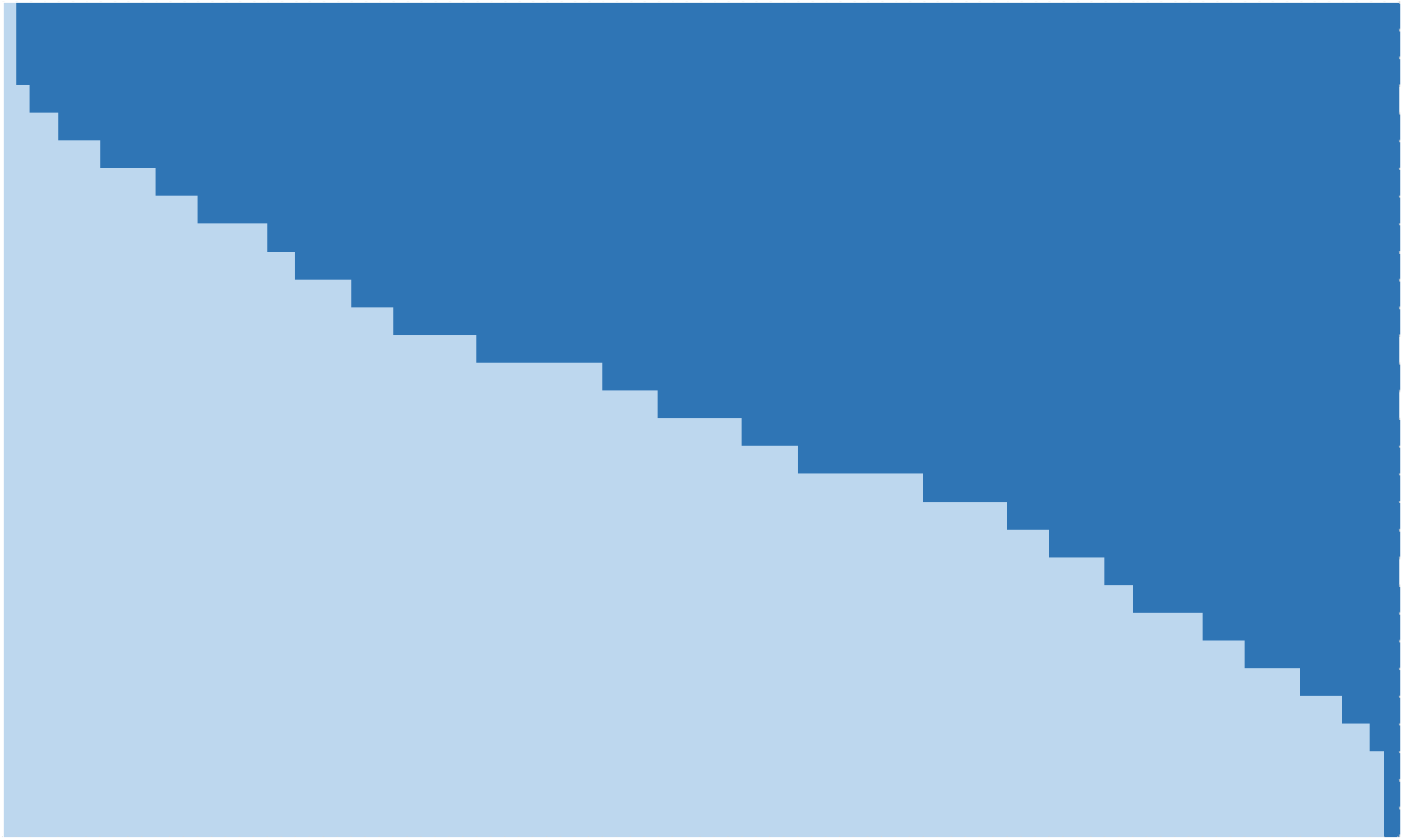


Solutions

- 30 clusters, $m = 100$
- Time effect modelled as a 6th order polynomial
- Designs achieving 90% power at the 5% significance level to detect the given effect size

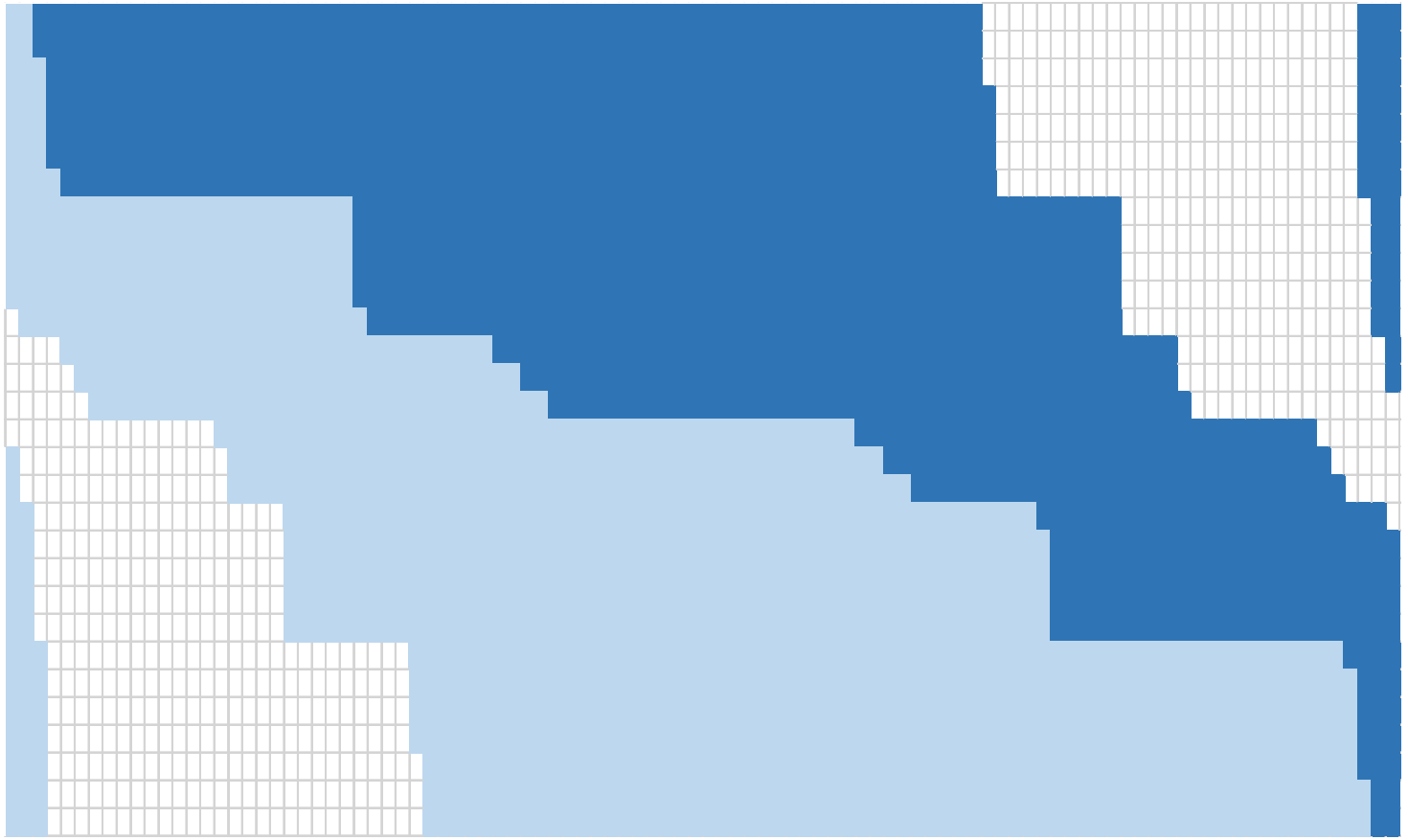
Effect size 0.15

n = 3,000



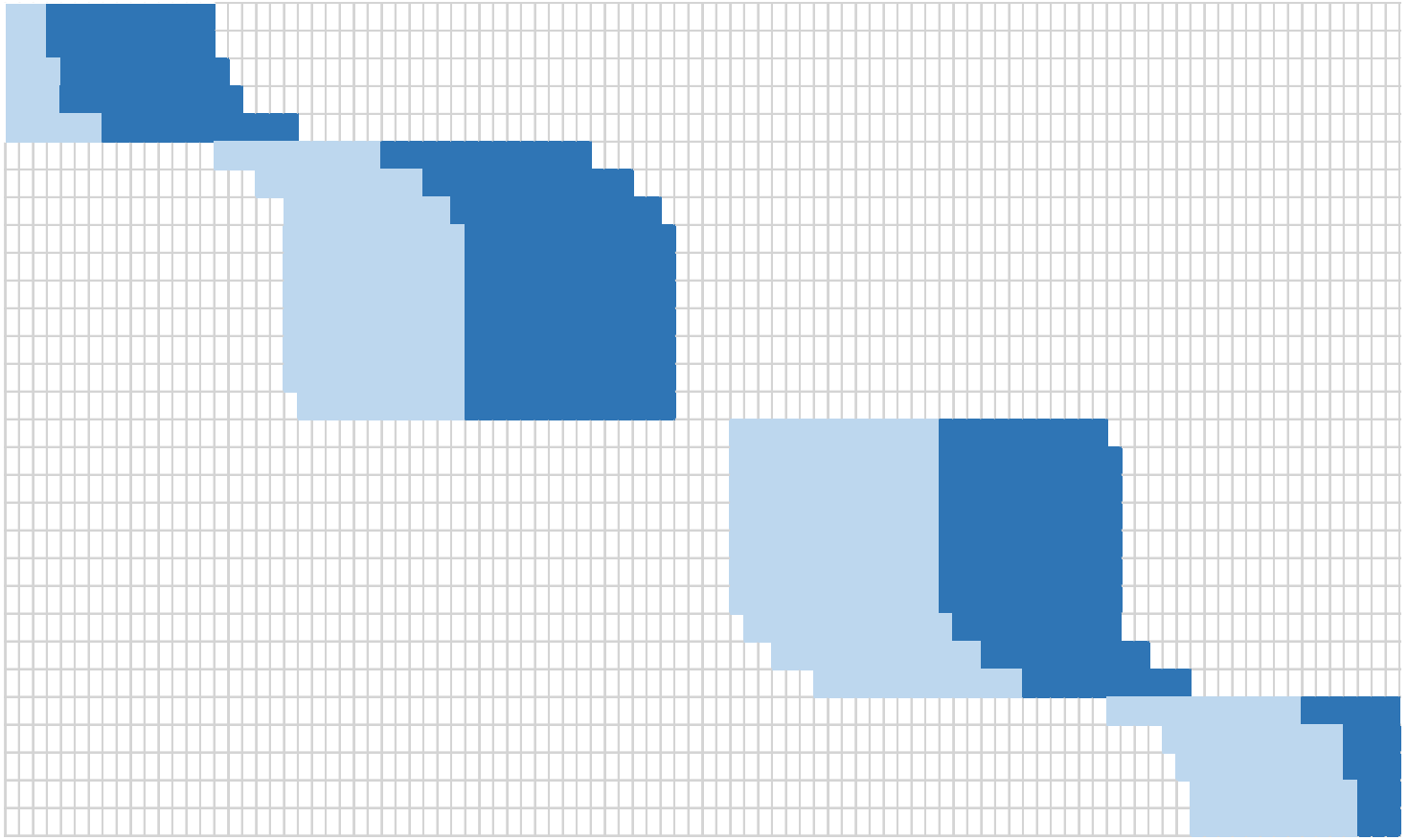
Effect size 0.20

n = 2,328



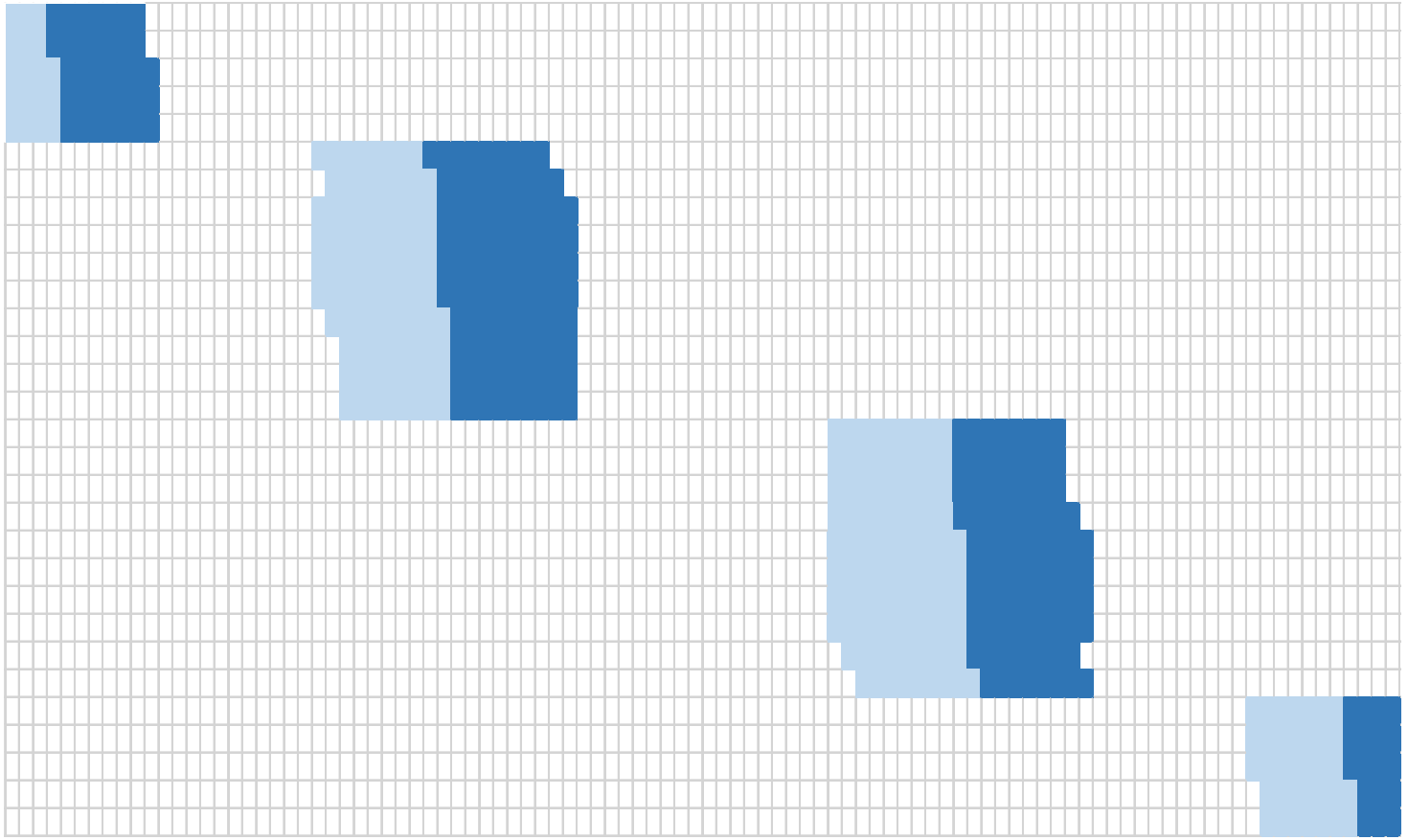
Effect size 0.25

n = 720



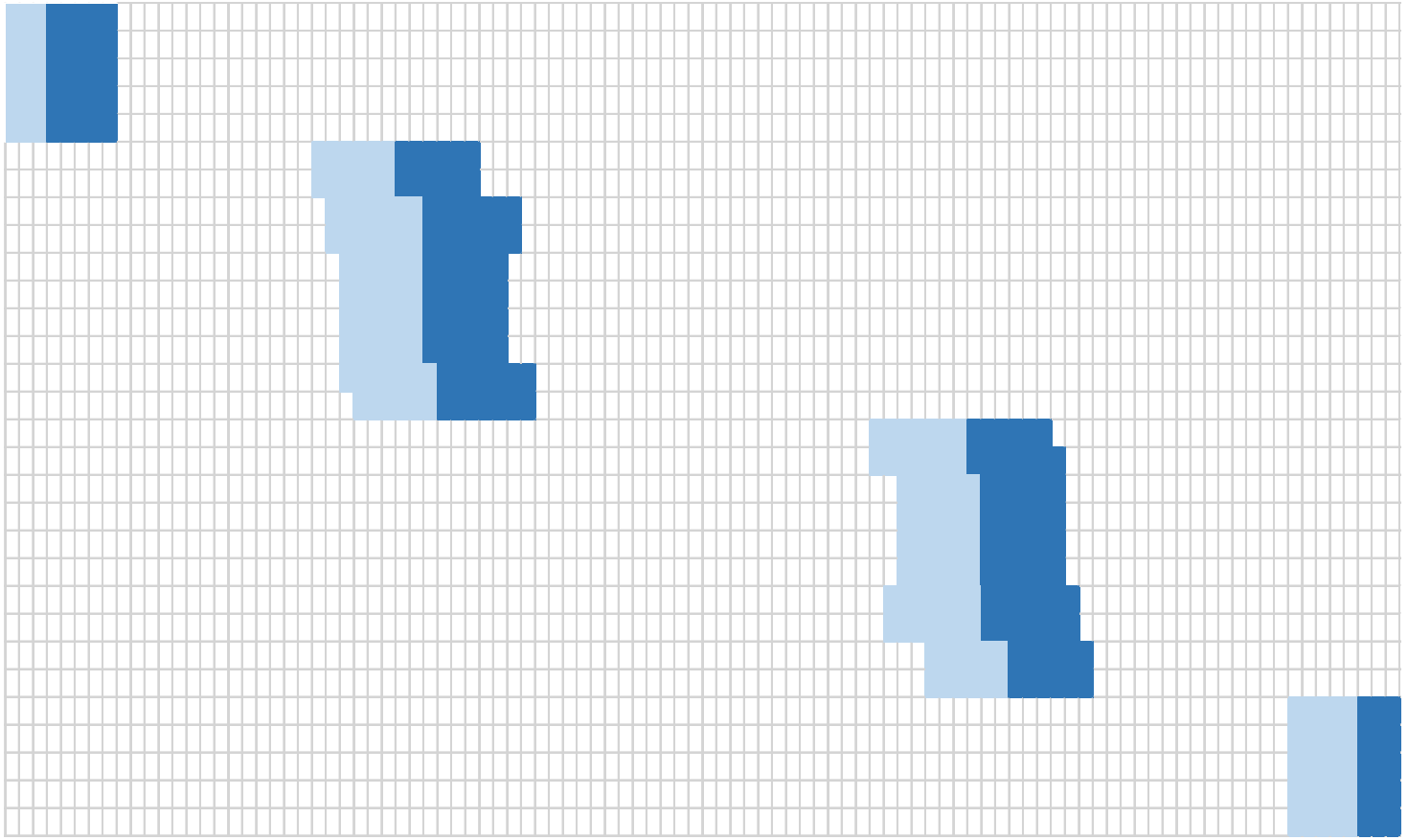
Effect size 0.30

n = 464



Effect size 0.35

n = 334



Concluding remarks

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- Cluster randomised trials with a prospective baseline: you can follow a simple rule of thumb
- Complete stepped wedge trials: you could argue for keeping the number of steps small, even with a large number of clusters
- Incomplete stepped wedge trials: you could argue for randomising clusters to a series of non-overlapping interrupted time series
- The less “smooth” the time effect, the more steps you may need

Concluding remarks

- I have ignored problems with small numbers of clusters: that's a whole other talk!
- Design needs new thinking, but analysis needs new software tools

Venue: **Whitechapel Gallery, London, UK** in-person, and also online
For more info: https://www.qmul.ac.uk/pctu/courses-and-events/

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Questions?

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