Methods: Mind the Gap
Webinar Series

Designing Stepped Wedge Trials with Continuous Recruitment

Presented by:
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• New ways of thinking for trials with continuous recruitment
• Some methods
• Some design problems
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Introduction
Equity and evidence during vaccine rollout: stepped wedge cluster randomised trials could help

bmj.com/content/372/bm...
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
The Gambia Hepatitis Intervention Study

The Gambia Hepatitis Study Group

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 are major health problems in 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
The Gambia Hepatitis Intervention Study

The Gambia Hepatitis Study Group

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

First we came up with a typology.

- People who use the term typology
- People who don’t use the term typology

fresh spectrum stepped wedge hog blog
ORIGINAL ARTICLE

Key concepts in clinical epidemiology: Stepped wedge trials
Richard Hooper*

Institute of Population Health Sciences, Queen Mary University of London, London, UK
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Repeated cross-section
Closed cohort
Continuous recruitment
New ways of thinking
COMMENTARY

Stepped wedge trials with continuous recruitment require new ways of thinking

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Continuous recruitment in a cluster

Time

Cluster 1
Continuous recruitment in a cluster

<table>
<thead>
<tr>
<th>Time</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Period 3</th>
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<tbody>
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Cluster 1

X
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

Cluster 1

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

\[ ICC = \rho \tau |t_2 - t_1|, \quad t = 0 \text{ at the start of the trial, and } t = 1 \text{ at the end} \]
3. Modelling the underlying effect of time

Cluster 1

Expected outcome

Time
3. Modelling the underlying effect of time

Cluster 1

Expected outcome

Time

Cluster 2

Expected outcome

Time
4. Allowing for a transition period

Cluster 1
4. Allowing for a transition period
4. Allowing for a transition period

Cluster 1

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

Cluster 1
Cluster 2
Cluster 3
Cluster 4
Cluster 5
Cluster 6
Cluster 7
Cluster 8
Cluster 9
Cluster 10
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 $\delta$ is the intervention effect
Generalised least squares estimation

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

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

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

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

$$\text{Var}(\hat{\boldsymbol{\theta}}) = (\mathbf{Z}' \mathbf{V}^{-1} \mathbf{Z})^{-1}$$
Simplification/regularisation of recruitment times

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

$0 \frac{1}{m} \frac{2}{m} \frac{3}{m} \frac{4}{m}$
Some design problems
• Cluster randomised trials with a prospective baseline
Optimal design of cluster randomised trials with continuous recruitment and prospective baseline period

Richard Hooper\textsuperscript{1} \textsuperscript{i}d and Andrew J Copas\textsuperscript{2} \textsuperscript{i}d
Cluster 1
Cluster 2
Cluster $J$
Cluster $J+1$
Cluster $J+2$
Cluster 2$J$

Linear effect of time
Cluster 1
Cluster 2
Cluster $J$
Cluster $J+1$
Cluster $J+2$
Cluster 2$
$

?  

Expected outcome

Time

Quadratic effect of time
Cluster 1
Cluster 2
Cluster J
Cluster J+1
Cluster J+2
Cluster 2J

Expected outcome vs. Time

Cubic effect of time
Cluster 1
Cluster 2
Cluster $J$
Cluster $J+1$
Cluster $J+2$
Cluster $2J$

Expected outcome

Time

Discontinuous effect of time
Variance of treatment effect estimator

$m = 100$

$\rho = 0.05$

$\tau = 0.5\quad$ linear

Cross-over

Variance

0   0.2   0.4   0.6   0.8   1

0.1   0.01
Variance of treatment effect estimator

\[ m = 100 \]
\[ \rho = 0.05 \]
\[ t = 0.5 \]

Linear, Quadratic, Cubic

![Graphs showing the variance of treatment effect estimator for linear, quadratic, and cubic models.](image)
Variance of treatment effect estimator

quartic

quintic

sextic
Variance of treatment effect estimator
Variance of treatment effect estimator

\[ \tau = 1.0 \quad \tau = 0.5 \quad \tau = 0.1 \]

\[ m = 25 \]

\[ m = 50 \]
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:

\[ \tau = 1.0: \quad m\rho \leq 1 \]
\[ \tau = 0.5: \quad m\rho \leq 2 \]
\[ \tau = 0.1: \quad m\rho \leq 5 \]
• Complete stepped wedge trials
Optimal stepped-wedge cluster randomised trial designs for non-uniform correlation structures

Michael J. Grayling¹, Richard Hooper², Kim May Lee³

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2. Pragmatic Clinical Trials Unit, Queen Mary University of London, London, UK
3. Institute of Psychiatry, Psychology & Neuroscience, King’s College London, London, UK
• Complete stepped wedge trials
  • \( m = 100 \)
  • Regularised recruitment times \( \frac{1}{100}, \frac{2}{100}, \frac{3}{100}, \ldots \)
  • 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
quadratic time effect

quartic time effect

quintic time effect
• Incomplete stepped wedge trials
The hunt for efficient, incomplete designs for stepped wedge trials with continuous recruitment and continuous outcome measures

Richard Hooper, Jessica Kasza and Andrew Forbes
- **Incomplete stepped wedge trials**

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[Diagram showing stepped wedge trials across clusters]
Search algorithm

1. Start with a complete design
2. Look for a more efficient variation with the same sample size
3. Remove the participant with the least influence on power
4. Look for a more efficient variation with the same sample size
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
Concluding remarks

• 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
8th ANNUAL MEETING
CURRENT DEVELOPMENTS IN CLUSTER RANDOMISED TRIALS & STEPPED WEDGE DESIGNS

14-15 NOVEMBER 2022

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


Hooper R. Key concepts in epidemiology: stepped wedge trials. J Clin Epi 2021;137:159-162


Grayling MJ, Hooper R, Lee KM. Optimal stepped wedge cluster randomised trial designs for non-uniform correlation structures. unpublished

Other useful references


Questions?

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