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INTRODUCTION TO STEPPED WEDGE CLUSTER RANDOMIZED DESIGNS

GARDENER'S GROVE CONFERENCE
28 March 2023

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OUTLINE

1. What is a stepped wedge cluster randomized trial (SW-CRT)?
2. Advantages of SW-CRTs
3. Disadvantages of SW-CRTs
4. Available resources
5. Conclusions

WHAT IS A STEPPED WEDGE CRT?

- Standard parallel arm cluster randomized trial (CRT):
  - Clusters randomized to either the intervention or control arm of the trial
- Stepped wedge cluster randomized trial (SW-CRT):
  - Clusters start the trial in the control condition
  - Clusters gradually cross over to the intervention in random order

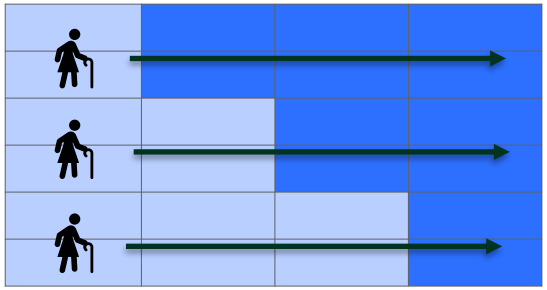
TYPICAL SW-CRT DESIGN

Randomize

Cluster	Period 1	Period 2	Period 3	Period 4	Period 5
1					
2					
3					
4					
5					
6					
7					
8					

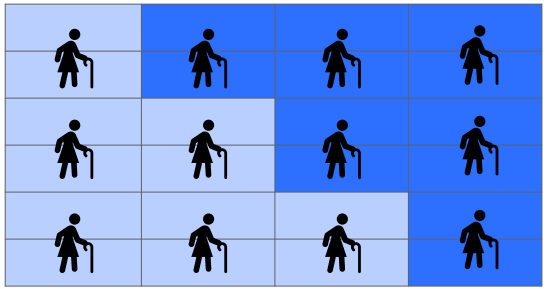
Control
Intervention

COHORT SW-CRT DESIGN



- All patients recruited in the first period
- All patients are followed to the last period
- All patients exposed to both the control and study intervention

CROSS-SECTIONAL SW-CRT DESIGN



- Different patients recruited every period of the trial
- Approximately half of the patients will be exposed to the control and half to the study intervention

A KEY CHARACTERISTIC OF CRTs

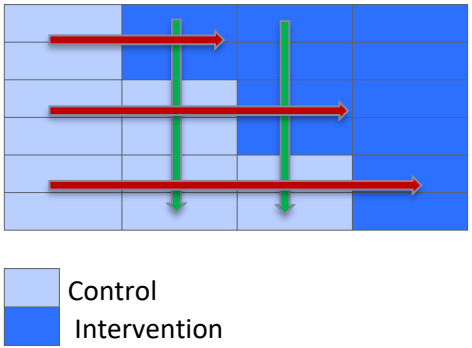
- Multiple observations from the same cluster are usually positively correlated
  - The strength of the correlation is measured by the Intracluster Correlation Coefficient (ICC)
- Failure to account for the ICC in the sample size calculation will yield sample size estimates that are too small
- Failure to account for the ICC in the analysis will yield p-values that are too small

TWO KEY CHARACTERISTICS OF SW-CRTs (1)

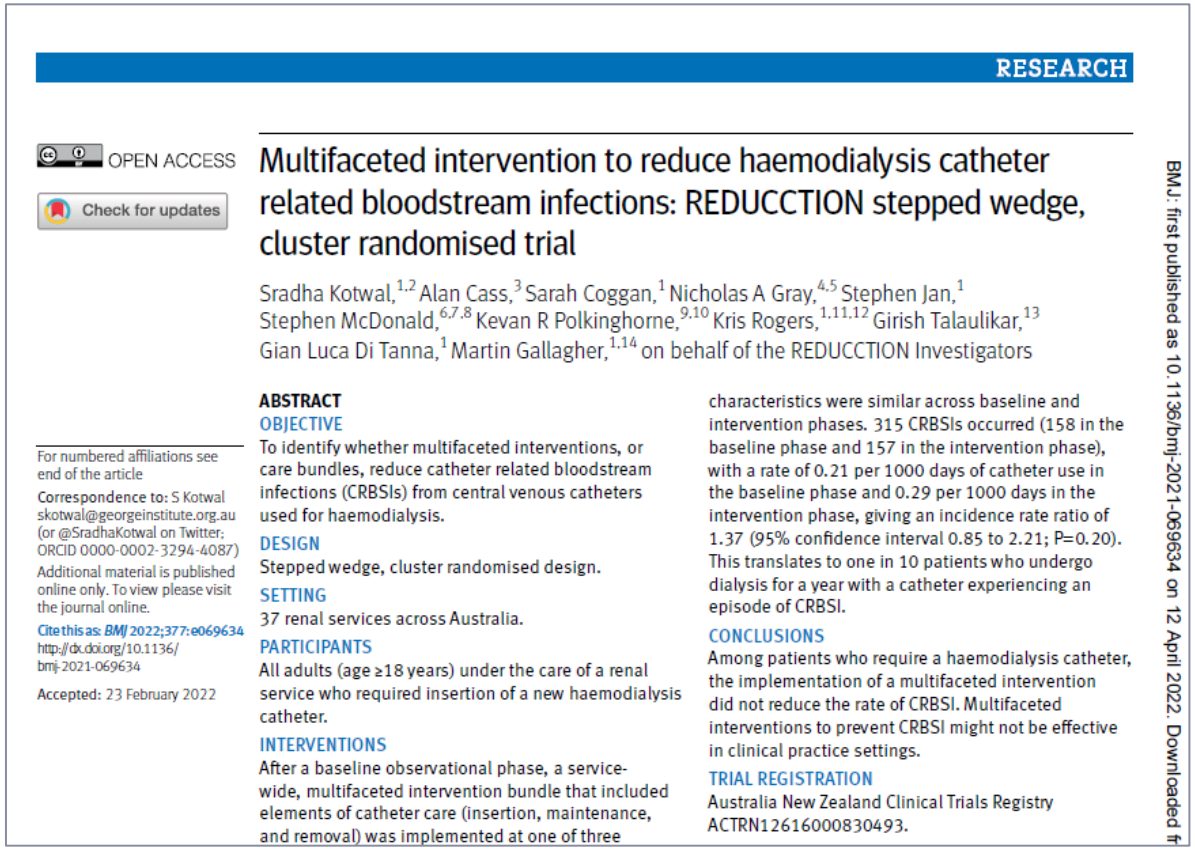
- Intracluster correlations are more complex
  - Within-period ICC: correlation among multiple individuals in the same cluster and same period
  - Between-period ICC: correlation among multiple individuals in the same cluster but different periods
- Failure to account for the correct correlation structure in the sample size calculation will yield sample size estimates either too large or too small
- Failure to account for the correct correlation structure in the analysis will yield p-values that are either too large or too small

TWO KEY CHARACTERISTICS OF SW-CRTs (2)

- Intervention effect is partially confounded with time *by design*
- Statistical analysis of the SW-CRT must always account for period as a covariate



EXAMPLE (1): CROSS-SECTIONAL DESIGN



OPEN ACCESS

Check for updates

Multifaceted intervention to reduce haemodialysis catheter related bloodstream infections: REDUCCTION stepped wedge, cluster randomised trial

Sradha Kotwal,[1,2] Alan Cass,[3] Sarah Coggan,[1] Nicholas A Gray,[4,5] Stephen Jan,[1] Stephen McDonald,[6,7,8] Kevan R Polkinghorne,[9,10] Kris Rogers,[1,11,12] Girish Talaulikar,[13] Gian Luca Di Tanna,[1] Martin Gallagher,[1,14] on behalf of the REDUCCTION Investigators

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Additional material is published online only. To view please visit the journal online.

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Accepted: 23 February 2022

ABSTRACT

OBJECTIVE

To identify whether multifaceted interventions, or care bundles, reduce catheter related bloodstream infections (CRBSIs) from central venous catheters used for haemodialysis.

DESIGN

Stepped wedge, cluster randomised design.

SETTING

37 renal services across Australia.

PARTICIPANTS

All adults (age ≥18 years) under the care of a renal service who required insertion of a new haemodialysis catheter.

INTERVENTIONS

After a baseline observational phase, a service-wide, multifaceted intervention bundle that included elements of catheter care (insertion, maintenance, and removal) was implemented at one of three

characteristics were similar across baseline and intervention phases. 315 CRBSIs occurred (158 in the baseline phase and 157 in the intervention phase), with a rate of 0.21 per 1000 days of catheter use in the baseline phase and 0.29 per 1000 days in the intervention phase, giving an incidence rate ratio of 1.37 (95% confidence interval 0.85 to 2.21; P=0.20). This translates to one in 10 patients who undergo dialysis for a year with a catheter experiencing an episode of CRBSI.

CONCLUSIONS

Among patients who require a haemodialysis catheter, the implementation of a multifaceted intervention did not reduce the rate of CRBSI. Multifaceted interventions to prevent CRBSI might not be effective in clinical practice settings.

TRIAL REGISTRATION

Australia New Zealand Clinical Trials Registry ACTRN12616000830493.

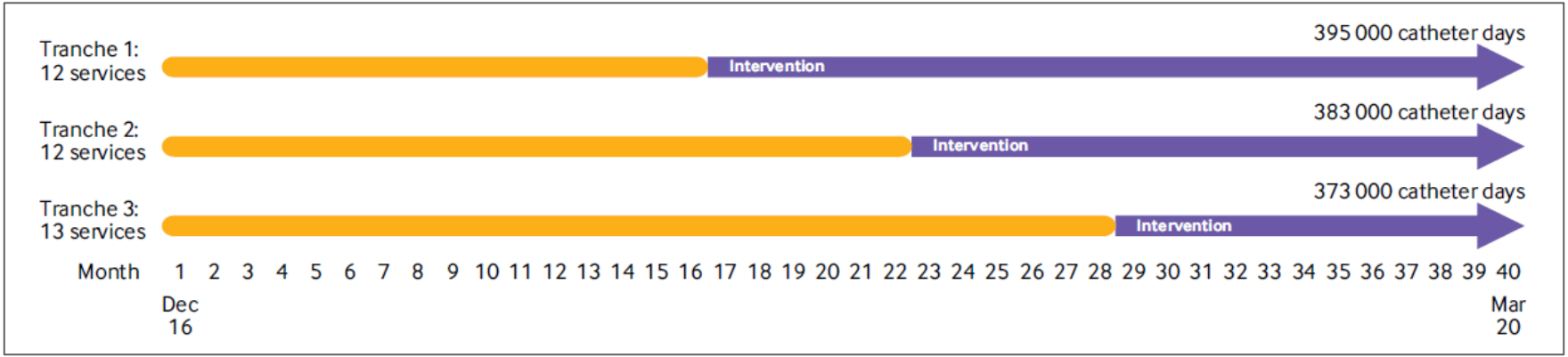
BMJ: first published as 10.1136/bmj-2021-069634 on 12 April 2022. Downloaded fr

EXAMPLE (1): CROSS-SECTIONAL DESIGN

- **Objective**: Does a multifaceted care bundle reduce catheter related bloodstream infections from central venous catheters used for hemodialysis?
- **Intervention:** A suite of recommendations regarding catheter care (insertion, maintenance, and removal)
- **Design:** SW-CRT involving 37 renal centers across Australia, randomized to implement the intervention at one of three time points
- **Participants**: 6364 unique patients requiring a new hemodialysis catheter during the study period (3519 control, 2845 intervention)
- **Primary outcome:** Rate of catheter-related bloodstream infections per 1000 days

EXAMPLE (1): CROSS-SECTIONAL DESIGN

- **Study design diagram**:



- **Randomization**: Covariate-constrained randomization was used to allocate the centers to one of three implementation time points

EXAMPLE (1): CROSS-SECTIONAL DESIGN

- **Results**:
  - Over 1.14 million catheter days were monitored
  - Raw event rate in the control periods: 0.32/1000 catheter days
  - Raw event rate in the intervention periods: 0.24/1000 catheter days
  - After accounting for period: IRR 1.37 (95% CI 0.85 to 2.21; p=0.20)

EXAMPLE 2: COHORT DESIGN

Nephrol Dial Transplant (2016) 31: 1302–1309
doi: 10.1093/ndt/gfv416
Advance Access publication 28 December 2015

ndt
Nephrology Dialysis Transplantation

Original Articles

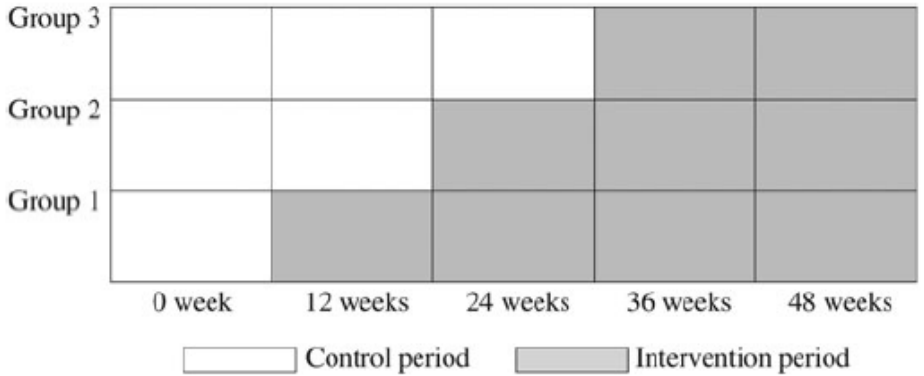
Effects of an intradialytic resistance training programme on physical function: a prospective stepped-wedge randomized controlled trial

Paul Norman Bennett[1,2], Steve Fraser[3], Robert Barnard[4], Terry Haines[5], Cherene Ockerby[6], Maryann Street[7], Wei Chun Wang[8] and Robin Daly[3]

[1]School of Nursing and Midwifery, Deakin University, Geelong, VIC, Australia, [2]Centre for Nursing Research, Western Health, Melbourne, VIC, Australia, [3]School of Exercise & Nutrition Sciences, Deakin University, Burwood, VIC, Australia, [4]South Australia Department of Health, Centre for Physical Activity in Ageing—Central Adelaide Local Health Network, Adelaide, SA, Australia, [5]Physiotherapy Department, School of Primary Health Care, Monash University and Monash Health, Monash, VIC, Australia, [6]Centre for Nursing Research, Deakin University & Monash Health Partnership, Monash, VIC, Australia, [7]Nursing and Midwifery Research Centre, Deakin University-Eastern Health, Box Hill, VIC, Australia and [8]School of Nursing and Midwifery, Deakin University, Burwood, VIC, Australia

EXAMPLE 2: COHORT DESIGN

- **Objective**: Does an individualized resistance training programme delivered by qualified exercise professionals during the first hour of hemodialysis treatment improve patients' physical function?
- **Design**: SW-CRT involving 15 community hemodialysis clinics (171 patients) randomized to implement the intervention at one of three time points.



EXAMPLE 2: COHORT DESIGN

- **Rationale:** “A SW was chosen to allow all participants the opportunity to participate in the intervention”
- **Outcomes**: Physical function, Blood pressure, Quality of life
- **Results**: Significant improvements in physical function and blood pressure, but quality of life could not be analyzed
- **Limitations**:
  - The need for repeated outcome assessment was burdensome for many participants and some measurements had to be dropped
  - The need for a lengthy control period led to many participants withdrawing from the trial

ADVANTAGES OF SW-CRTs

MAIN ADVANTAGES

- May facilitate cluster recruitment when all clusters are offered the intervention during the trial
- May be more powerful (require fewer clusters) than a parallel arm CRT design
- Yields more robust evidence when the only other alternative is a before and after design

DISADVANTAGES OF SW-CRTS

MAIN DISADVANTAGES

- Increased risks of bias over parallel arm CRTs
- More complicated to analyze and interpret
- May increase the total duration of the study
- Heavy data collection burden
- Methods not yet fully developed
- Logistical complexities

Hemming K, Taljaard M. Reflection on modern methods: when is a stepped-wedge cluster randomized trial a good study design choice? Int J Epidemiol. 2020 Jun 1;49(3):1043-1052.

Planned…

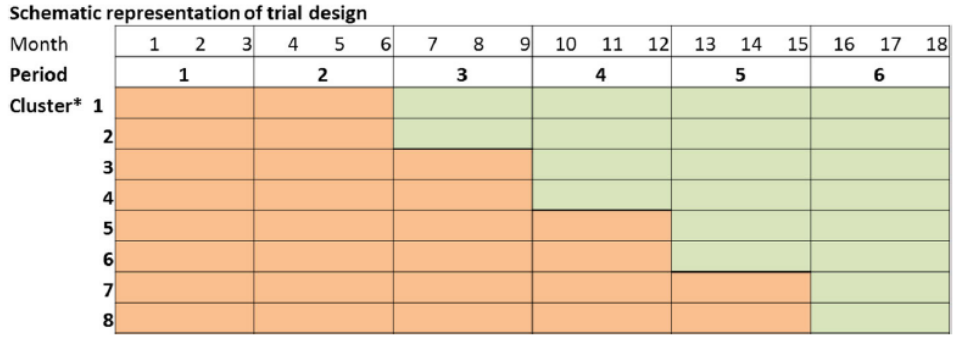


Fig. 1 Schematic representation of the planned stepped wedge, cluster randomized trial study design. *Orange boxes*, cluster not exposed to intervention. *Green boxes*, cluster exposed to intervention. * Participating units were to be randomized to clusters 1–8 and would all start with a control period. Every 3 months, two units would cross over to use the intervention

Realized…

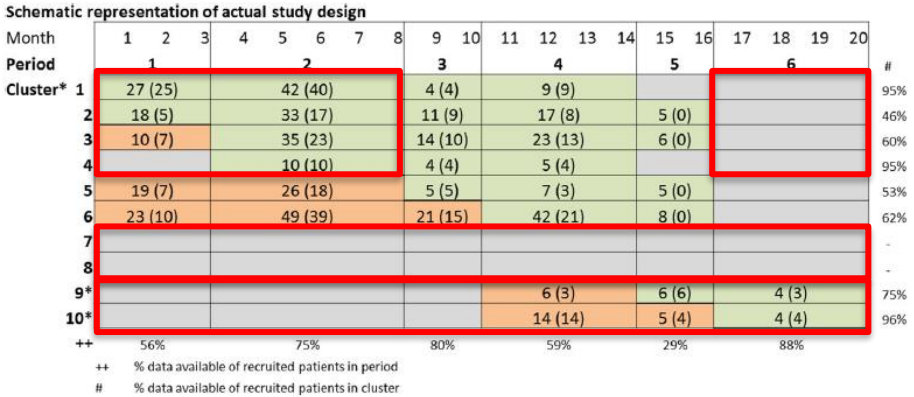


Fig. 3 Schematic representation of the inclusion of patients per period in each cluster in the actual study design of the stepped wedge, cluster randomized trial. *Orange boxes*, cluster not exposed to intervention. *Green boxes*, cluster exposed to intervention. *Beige boxes*, cluster in which no patients were included in the specified period. * Participating units 1–10 were randomized to clusters subsequently starting to use the intervention

Heim ea. HELP! Problems in executing a pragmatic, randomized, stepped wedge trial on the Hospital Elder Life Program to prevent delirium in older patients. *Trials* **18,** 220 (2017)

ELSEVIER

Journal of Clinical Epidemiology 148 (2022) 93–103

Journal of Clinical Epidemiology

ORIGINAL ARTICLE

Recruitment and implementation challenges were common in stepped-wedge cluster randomized trials: Results from a methodological review

Agnes Caille[a,b,c,*], Monica Taljaard[d,e], Floriane Le Vilain—Abraham[b,c], Alexis Le Moigne[a], Andrew J. Copas[f], Florence Tubach[a,1], Agnes Dechartres[a,1]

[a]*Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Pitié-Salpêtrière, Département de Santé Publique, Paris, France*

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Accepted 20 April 2022; Published online 26 April 2022

At least one implementation challenge reported in 44% of 55 SW-CRTs published 2019-2020

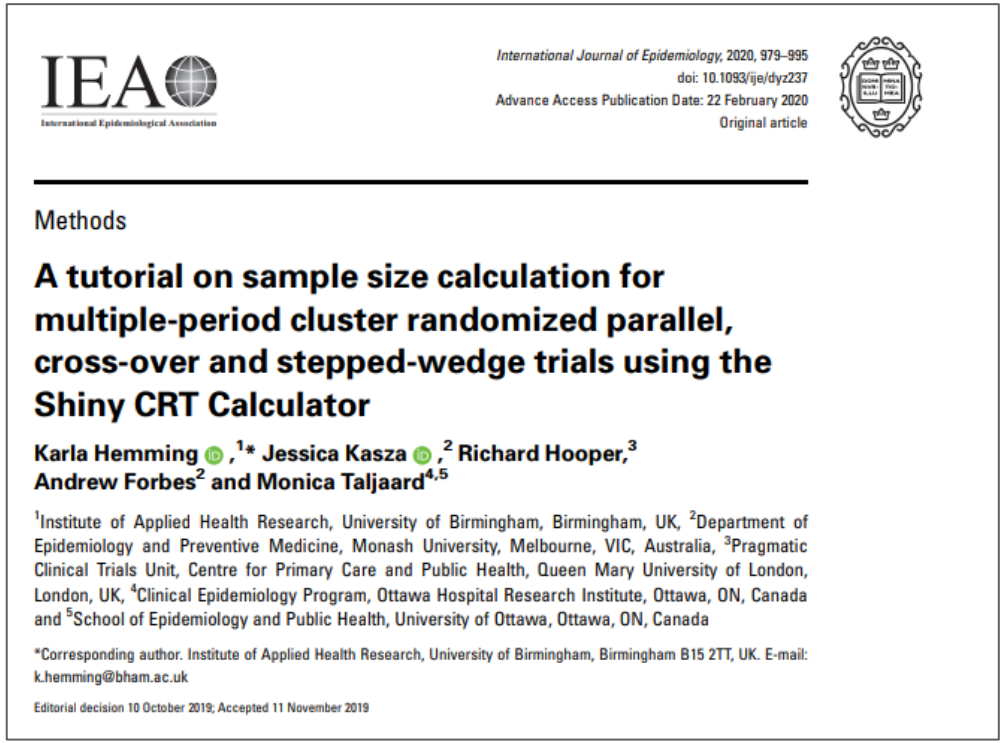
AVAILABLE RESOURCES

- At least 18 sample size calculators for SW-CRTs available currently, on a variety of platforms including:
  - Excel
  - SAS
  - R and RShiny
  - STATA
  - PASS
  - NQuery Advisor
- These vary substantially in the functionality and types of design features they support

Yongdong Ouyang, Fan Li, John S Preisser, Monica Taljaard, Sample size calculators for planning stepped-wedge cluster randomized trials: a review and comparison, *International Journal of Epidemiology*, 2022;, dyac123, https://doi.org/10.1093/ije/dyac123

SHINY CRT SAMPLE SIZE CALCULATOR

- https://clusterrcts.shinyapps.io/rshinyapp/



International Journal of Epidemiology, 2020, 979–995
doi: 10.1093/ije/dyz237
Advance Access Publication Date: 22 February 2020
Original article

Methods

A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator

Karla Hemming [1]*, Jessica Kasza [2], Richard Hooper [3], Andrew Forbes [2] and Monica Taljaard [4,5]

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK, [2]Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia, [3]Pragmatic Clinical Trials Unit, Centre for Primary Care and Public Health, Queen Mary University of London, London, UK, [4]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada and [5]School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

*Corresponding author. Institute of Applied Health Research, University of Birmingham, Birmingham B15 2TT, UK. E-mail: k.hemming@bham.ac.uk

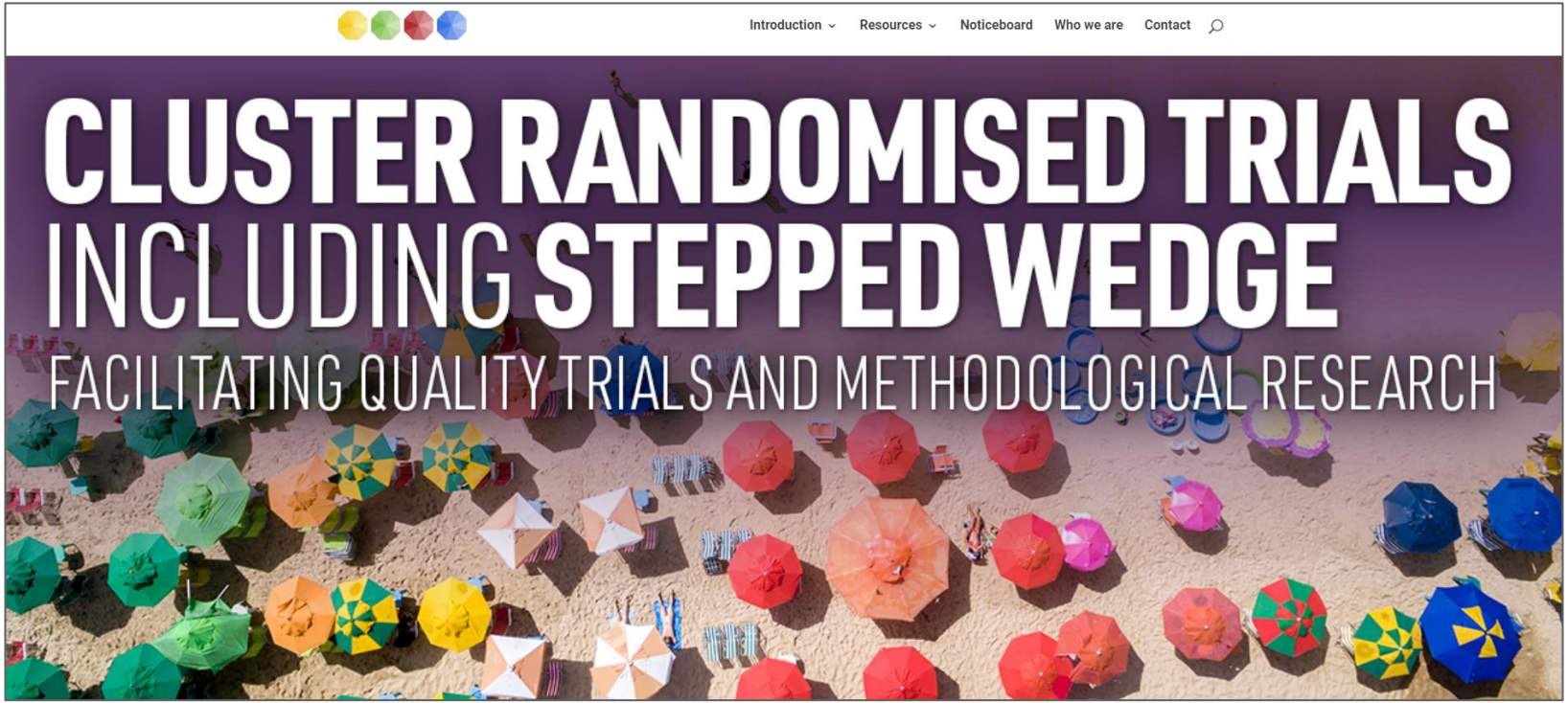
Editorial decision 10 October 2019; Accepted 11 November 2019

NIH SW CALCULATOR

- https://researchmethodsresources.nih.gov/Tools

QMUL CLUSTER RANDOMIZED TRIALS SITE

- https://clusterrandomisedtrials.qmul.ac.uk/



WHEN SHOULD YOU CONSIDER A SW-CRT?

IEA International Epidemiological Association

International Journal of Epidemiology, 2020, 1043–1052
doi: 10.1093/ije/dyaa077
Advance Access Publication Date: 9 May 2020
Education Corner

Education Corner

Reflection on modern methods: when is a stepped-wedge cluster randomized trial a good study design choice?

Karla Hemming [1,*] and Monica Taljaard[2,3]

[1]Institute of Applied Health Research, University of Birmingham, Birmingham, UK, [2]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada, [3]School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada

NARRATIVE REVIEW

OPEN ACCESS

Cutting edge or blunt instrument: how to decide if a stepped wedge design is right for you

Richard Hooper, Sandra M Eldridge

BMJ Qual Saf: first published as 10.

Richard Hooper's blog: A website devoted to stepped wedge trials. (https://steppedwedgehog.blog/)

https://rethinkingclinicaltrials.org/news/grand-rounds-ethics-and-regulatory-series-december-9-2022-the-stepped-wedge-cluster-randomized-trial-friend-or-foe-monica-taljaard-phd-david-magnus-phd/

CONCLUSIONS

- The SW-CRT is a novel type of CRT design that has been enthusiastically embraced by trialists
- It raises several complications in the design and analysis and is vulnerable to increased risks of bias
- Still requires substantial methodological development
- Need a clear rationale for choosing a SW-CRT
- When feasible, individual randomization or a parallel arm CRT is usually preferable