Design and Analysis of Stepped Wedge Cluster Randomised Trials

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Declarations

Originality

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

Authorship and Collaboration

I hereby certify that the work embodied in this thesis has been done in collaboration with other researchers and contains published papers of which I am a joint author. I have included as part of the thesis written statements, endorsed by my supervisor, outlining the extent of collaboration and my contribution to the joint publications.

Thesis by Publication

I hereby certify that this thesis is in the form of a series of four papers. I have included as part of the thesis in the appendices a written statement from each co-author, endorsed in writing by the Faculty Assistant Dean (Research Training), attesting to my contribution to any jointly authored papers.

SIGNED:_____

Mr. Daniel Barker

University of Newcastle

February 2017

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List of Manuscripts

This thesis contains the following manuscripts in sequential order, which make up Chapters 2 through 5.

D. Barker, P. McElduff, C. D'Este, M. J. Campbell, *Stepped wedge cluster randomised trials: a review of the statistical methodology used and available.* BMC Medical Research Methodology, 2016. **16**(1): p. 69. DOI: 10.1186/s12874-016-0176-5

D. Barker, C. D'Este, M. J. Campbell, P. McElduff, *Minimum number of clusters and comparison of analysis methods for cross sectional stepped wedge cluster randomised trials with binary outcomes: A simulation study.* BMC Trials (accepted 27th February 2017)

D. Barker, P. McElduff, M. J. Campbell, C. D'Este, *Cross sectional stepped wedge cluster randomised trials with binary outcomes: Are approximations leaving us short on power?* Statistical Methods in Medical Research (Under Review)

D. Barker, C. D'Este, P. McElduff, *Statistical considerations for estimating power of stepped wedge cluster randomised trials with cohorts of participants and a binary outcome.* Contemporary Clinical Trials (Under Review)

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Glossary of Terms

RCT	Randomised Controlled Trial
CRT	Cluster Randomised Trial
ICC	Intra-cluster Correlation Coefficient
GLMM	Generalised Linear Mixed Model
GEE	Generalised Estimating Equation
RVE	Robust Variance Estimator
DE	Design Effect
CV	Coefficient of Variation
SW-CRT	Stepped Wedge Cluster Randomised Trial
CIPHER	Centre for Informing Policy in Health with Evidence from Research
CRE	Centre for Research Excellence
SPIRIT	Supporting Policy In health with Research: an Intervention Trial
SWD	Stepped Wedge Design
CRCT	Cluster Randomised Controlled Trial
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
CINAHL	Cumulative Index to Nursing and Allied Health Literature
PH	Proportional Hazards
ANCOVA	ANalysis of COVAriance
ANOVA	ANalysis of VAriance
LMM	Linear Mixed Model
HH	Hussey and Hughes
OR	Odds Ratio

Abstract

This thesis explores aspects of the design and analysis of stepped wedge cluster randomised trials from a statistical viewpoint. It contains a review of current research practices when the design is used in the field and also explores the existing methodological research into the design. It was found that stepped wedge trials often have few clusters (45% < 10 clusters) and a binary outcome (62%). Following this there are three simulation studies presented that aim to explore the use of binary outcome measures in stepped wedge trials with few clusters.

The first simulation study examines the different ways in which data from a stepped wedge cluster randomised trial with repeated cross-sections might be analysed. This study also explores the minimum number of clusters needed for consistent and reliable inference under ideal circumstances: such as equal cluster sizes, a time trend that is truly linear, and an intervention effect that is identical for every cluster. For a stepped wedge cluster randomised with 3 steps we found that randomising less than 6 clusters led to estimation problems for all methods of analysis.

The second simulation study compares the existing power and sample size determination method for stepped wedge cluster randomised trials to the statistical power of simulated data using the same assumptions. The aim of this study was to see how well the use of Normal approximations in the case of a binary outcome worked for formula based approaches when few clusters were available for analysis. As these approximations became less appropriate, formula based approaches consistently overestimated stepped wedge trial power.

The final simulation study is about stepped wedge cluster randomised trials in which cohorts of participants are repeatedly measured. Both closed cohorts, where the same participants are followed throughout the trial, and open cohorts, where participants may enter into the trial at any point, are considered. The effect on study power of different values for the level two and level three variation for both designs is explored. Given the same number of participants per cluster per time, there was generally little difference between the open cohort and closed cohort design for the correlation values we used.