Health economic evaluation alongside stepped wedge trials:

a methodological systematic review

Thomas Lung[1, 2], Lei Si[1], Richard Hooper[3] & Gian Luca Di Tanna[1]

1. The George Institute for Global Health, University of New South Wales, Sydney, New South Wales, 2042, Australia
2. Faculty of Medicine and Health, School of Public Health, Edward Ford Building A27, University of Sydney, Sydney, NSW, 2006, Australia
3. Institute of Population Health Sciences, Queen Mary University of London, London, UK

Thomas Lung https://orcid.org/0000-0001-9978-6311, Lei Si https://orcid.org/0000-0002-3044-170X, Richard Hooper https://orcid.org/0000-0002-1063-0917, Gian Luca Di Tanna https://orcid.org/0000-0002-5470-3567

Corresponding author: Gian Luca Di Tanna, Email: GDiTanna@georgeinstitute.org.au

Abstract

Background: Recently, there has been an increase in use of the stepped wedge trial (SWT) design in the context of health services research, due to its pragmatic and methodological advantages over the parallel group design. Our objective was to summarise the statistical methods used when conducting economic evaluations alongside SWTs.

Methods: A systematic literature search extending to February 2020 was conducted in the PubMed, Scopus, Cochrane and NHS-EED databases to find and evaluate studies where there was an intention to conduct an economic evaluation alongside a SWT. Studies were assessed for their eligibility, findings, reporting of statistical methods and quality of reporting.

Results: Of the 586 studies retrieved from the literature search, 69 studies were identified and included in this systematic review. 54 studies were published protocols, with eight economic evaluations and seven studies reporting full trial results. Included studies varied in terms of their reporting of statistical methods, in both detail and methodology. There were 34 studies that did not report any statistical methods for the economic evaluation and only 16 studies reported appropriate methods, mainly using some form of mixed/multilevel models and two used seemingly unrelated regression. 12 studies reported the use of generic bootstrap methods and other modelling techniques whilst the remaining studies failed to appropriately account for clustering, correlation or adjusted for time.

Conclusions: The use of appropriate statistical methods that account for time, clustering, and correlation between costs and outcomes is an important part of SWT health economics analysis that will benefit from an effort in communicating the methods available and their performance.

Key points for Decision Makers

- In this methodological systematic review we have identified 69 papers reporting stepped wedge trials protocols (n=54), results (n=7) or economic evaluations (n=8).
- Statistical methods of economic evaluations alongside stepped wedge trials were often poorly reported, lacking detail and methodology. Only 16 studies reported the use (or intention to use) multilevel/mixed models, 2 seemingly unrelated regression and 8 generic bootstrap.
- It is important that appropriate statistical analyses that account for time, clustering and correlation between costs and outcomes - such as bivariate multilevel/mixed models, seemingly unrelated regressions, and the two-stage bootstrap method – are used.

Background

The stepped wedge randomised trial (SWT) design is an alternative to a parallel cluster-randomised trial design that is increasing in popularity in recent years. In brief, a stepped wedge trial design is a multi-arm, cluster randomised, cross-over design where the only cross-over that is permitted is unidirectional: from the control or routine care condition to the active intervention [1]. In the most common design, all clusters begin in the control condition, before crossing over at regular intervals (periods) to receive the intervention in a randomised order. This process continues until all clusters are exposed to the intervention.

Due to its pragmatic design, the SWT design has been used to assess the effect of new interventions in real-world settings (such as in hospitals, clinics or communities) where simultaneous implementation across all clusters is not possible for logistic, financial or ethical reasons [2-5]. To determine the effectiveness of an intervention, it is important to understand several key elements: how participants are recruited and followed-up in a trial; the length of time between successive crossover points and how the outcomes are collected. These elements can differ depending on how the stepped wedge design is implemented, hence the importance of transparency in published protocols and when presenting trials' results as indicated in the Consolidated Standards of Reporting Trials (CONSORT) extension checklist for SWTs [1].

A stepped wedge design may be chosen in preference to a parallel group cluster randomised design for reasons of practicality or statistical efficiency [6, 7]. On the other hand, ensuring that clusters comply with the complex schedule of a stepped wedge design requires a kind of 'extreme coordination' [8], and prolonging the study timetable so that participants are identified after clusters have been randomised introduces new risks of bias [9, 10].

Statistical methods for economic evaluations (EE) alongside cluster randomised controlled trials have recommended addressing clustering in both costs and outcomes as well as

correlation between individual- and cluster-level costs and outcomes [11-15]. A previous systematic review showed that most EEs alongside cluster randomised trials ignored clustering or correlation, leading to inaccurate point estimates [12] and potentially misleading conclusions about a studies cost-effectiveness [13].

An additional methodological challenge to consider in a SWT design is to adjust for the potential confounder of calendar time [4, 16]. However, the use of statistical methods in EE conducted alongside SWTs have hitherto not been systematically explored. We aim to systematically review EE alongside SWTs to examine statistical methods used to adjust cost and outcome variables for clustering and time effects inherent to the stepped wedge design.

Methods

Definition of stepped-wedge trial designs

We categorised the included studies into four main SWT designs, primarily using Copas et al.'s [17] definition.

Closed cohort: participants are identified and recruited at the beginning of the trial and participate continuously from the beginning until the end, without changing cluster, with their outcomes assessed at a series of follow-up times (typically pre-specified).

Open cohort: some participants are identified and recruited into the study from the beginning, others may become eligible and are recruited into the various clusters throughout the course of the study period, whilst some participants leave the trial prior to the conclusion of the study.

Continuous recruitment with short exposure (CRSE): As the name suggests, individuals become eligible and the recruitment is continuous as the study proceeds, with few (or even no) individuals recruited in the beginning. The main difference between CRSE and OC is that in the CRSE design, individuals are exposed to the intervention (or control) for only a short period

of time. The outcome of interest is often measured after a follow-up period; single or repeated measurements or time-to-event from the beginning of their exposure period.

Repeated cross-section design: A variation to the CRSE, whereby instead of continuous recruitment, participants are recruited at discrete time points, otherwise known as (vertical) cross-sections, with each cross-section acting as discrete snapshots at given times.

Systematic review

This systematic review considered all studies that reported the intent to (through a protocol) or conduct of EE alongside or based on data from SWTs. Literature searches extending to February 2020 were conducted in biomedical databases including PubMed, Scopus and the Cochrane Library as well as the National Health Service Economic Evaluation Database (NHS-EED) up to the 1st February 2020. Search terms were comprised of key words of SWT and health economics evaluation such as "step wedge", "phased implementation", "cost-effectiveness analys*", "cost-utility analys*" and "economic evaluation". A complete search strategy used in PubMed is provided in the Electronic Supplementary Appendix. Studies were excluded if: there was no mention of EE, conducted a cost minimisation or cost-consequence analysis, only a published abstract was available, the published study protocol was later updated with a published economic evaluation, or the study was not in English. References in the studies identified were searched manually to minimise the risk of exclusion of relevant citations (snowball inclusion).

First-round screening of titles and abstracts was independently screened by two investigators (TL & LS) using the following inclusion criteria: (i) use of the SWT design and (ii) EE as part of the research question(s) in the study. Second-round full-text screening was performed by three independent reviewers (TL, LS & GLDT), and disagreements around inclusion or exclusion were resolved by discussion and consensus between the three reviewers.

Trial and EE-specific information were extracted using pre-designed data extraction tables in Microsoft Excel. Trial information included the type of SWT (as defined earlier), the number of clusters/periods/participants and duration of the trial, the country that the study was conducted in, intervention and control details and primary outcome/s of the trial. The type (cost-benefit analysis, cost-effectiveness analysis or cost-utility analysis), outcomes (clinical endpoint, health unit or health-related quality of life), costs collected and statistical methods of conducting the EE were also extracted.

This systematic review adhered to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [18] and the quality of reporting studies that conducted EE were appraised against the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 24-item checklist [19]. We assessed the statistical methods of studies that reported EE results using a modified checklist from Gomes et al. [12]. The checklist focused on EE in SWT-specific issues, including whether: sample size calculations incorporated clustering in outcomes and costs ; clustering was recognized in the univariate analysis of incremental outcomes and costs; accounted for correlation between costs and outcomes; simultaneously accounting for clustering and correlation when estimating incremental cost-effectiveness; and adjustment for time in their analysis.

Results

Characteristics of the studies

A total of 531 references were identified from the electronic databases. After removal of duplicates, 503 titles and abstracts were screened. Based on our inclusion criteria, 80 articles were included for full-text assessment, of which 69 were included in the review. Figure 1 shows

the PRISMA flowchart, highlighting the identification, screening, eligibility and inclusion of studies.

Table 1 summarises the study characteristics and the analytical approach used of the 69 included studies. All four types of SWT designs were represented in this systematic review, however studies were mixed in terms of providing details around the trial design. Of the 69 included studies, 36 (52%) studies used a closed cohort design [20-55], 18 (26%) studies used a continuous recruitment with short exposure [56-73], eight (12%) used an open cohort [74-81] and seven (10%) used a repeated cross-section design [82-88]. 44 (64%) of the studies were published from 2017 onwards, reflecting an increasing uptake in the SWT methodology (see Figure 2). The studies conducted SWTs in: Europe (n=35, 51%), Australia (n=16, 23%), North America (n=8, 12%), Africa (n=5, 7%), Asia (n=4, 6%) and South America (n=1, 1%).

Of the 69 included studies, 54 (78%) were SWT protocols, seven (10%) reported the findings from both the SWT and EE and eight (12%) detailed the EE alone. Cost-effectiveness analysis (n=46) was the most commonly used type of EE, followed by cost-utility analysis (n=43) and cost-benefit analysis (n=4). 24 (35%) studies used both cost-effectiveness and cost-utility analysis and one (1%) study conducted both cost-utility and cost-benefit analysis. Two (3%) protocol studies did not report the type of EE that they planned to conduct.

Statistical methods of economic evaluations

34/69 (49%) studies did not report any statistical methods, of which 31/34 (91%) studies were SWT protocols [20-22, 25, 26, 29, 33, 37, 40-43, 45, 46, 50, 56, 58-60, 70-75, 77, 82-85, 87], 2/34 (6%) full EE [34, 80] and 1/34 (3%) trial results study [81]. The remaining protocol (23/54) and full EE and trial results (12/15) studies that reported statistical methods varied in both detail and methodology. A total of 16 studies (9/23 (39%) protocols and 7/12 (58%) EE and trial results) reported methods that accounted for time, clustering and correlation between

costs and outcomes by means of mixed/multilevel models [23, 24, 28, 30, 32, 35, 36, 38, 47, 51, 53-55, 57, 65, 79]. 13 of these were based on closed cohort type of SWT, two on CRSE and one was a protocol of an Open Cohort study.

2 trial studies reported the use of seemingly unrelated regression, one was a CC the other a CRSE. 8 papers (seven protocol, one trial results) discussed or used generic bootstrap, four of which was based on a CC type of SWT the other four on a CRSE design. 4 studies described the use of modelling techniques such as Bayesian techniques with Monte Carlo simulation (one protocol), Markov models (one protocol), decision trees (one EE) or generic probabilistic sensitivity analysis (one protocol). 4 protocol studies discussed generic regression methods (likely failing to take into account clustering, time trends and/or correlation between costs and outcomes) and one EE reported the use of empirical estimates of costs and effectiveness results.

Quality/reporting assessment

The total and individual CHEERs checklist scores of the eight EE studies identified by the systematic review are presented in Figure 3 and the Electronic Supplementary Appendix. In general, there was good adherence to best practice reporting standards, with all studies reporting 15 out of 24 items on the checklist. Four studies failed to characterise population heterogeneity in its presentation of costs, outcomes or cost-effectiveness [57, 78, 80, 88] and individual studies failed to report: EE in its title and how preference based outcomes were measured and valued [28]; the time horizon and discount rate [57]; characterising of uncertainty [88] and whether study authors had existing conflicts of interest [78].

Table 2 presents disaggregated results of whether the 15 studies that reported trial results and EE and EE alone met the criterion for statistical methods of the modified checklist. Studies did not provide enough detail to determine whether clustering was accounted for in the univariate analysis of costs 7/15 (47%) and 4/15 outcomes (27%). Similarly, in 6/15 (40%) of the studies,

it was unclear whether the statistical analysis accounted for correlation between costs and outcomes and in their estimation of incremental cost-effectiveness. 2/15 (13%) of studies did not take explicitly make appropriate assumptions about the distributions of costs and outcomes. In 4/15 (27%) and 6/15 (40%) of the studies it was difficult to determine whether appropriate assumptions were made about the distribution of costs, and outcomes, respectively. Finally, 3/15 (20%) of studies did not adjust for time in their analysis and 7/15 (47%) did not provide enough detail.

Discussion

The SWT design is increasing in popularity due to its potential to evaluate interventions in a 'real world' or health policy context. However, due to its rather complicated design (at least in terms of the statistical methodology to be used for the analyses), it is important that studies apply the proper statistical analyses in order to generate appropriate conclusions around an interventions' cost-effectiveness [6]. To our knowledge, this is the first systematic review to investigate the statistical methodology of planned and conducted EE of SWTs to date. There was a lack of detail in describing the design of the SWT. Similarly, the reporting of statistical methods associated with the EE was often non-existent and among the 35 (out of the 69) that reported this essential information, 17 did not use appropriate statistical methods, failing to consider critical elements of a SWT such as time, clustering and correlation between costs and outcomes.

Our systematic review finds the studies that conducted EE have been transparent in its reporting when judged against the CHEERS checklist, however did poorly when judged against our SWT-specific checklist, with 6 studies not reporting, or using inappropriate statistical methods to account for the SWT design. This is a finding echoed by a similar review of EE methods alongside cluster randomised trials, revealing a relative lack of attention given to statistical

methods for EE with no evidence of improvement over time [12]. More emphasis on transparency and reporting of statistical methods of future EE alongside SWTs will be required in order to avoid the same trend. Similar to the CONSORT extension checklist [1], we propose that an extension to the checklist is required to specifically address reporting around the statistical methods of EE, particularly for complex trial designs.

A simulation study of EE alongside cluster randomised trials (CRT) proposed five potential methods to be used: multilevel models (MLMs), seemingly unrelated regression (SUR), generalised estimating equations, the two-stage bootstrap and Monte Carlo simulations [15]. More recently another simulation study has shown that failing to take into account the clustered structure of the data in trial based economic evaluations using for instance ordinary least squares regression rather than MLMs leads to a substantial underestimation of the amount of variation [89]. We would also like to highlight that authors have seldomly specified the term bivariate (mixed/multilevel) model to explicitly acknowledge the (potential) correlation between costs and effectiveness data.

Accounting for secular and within-cluster trends is an additional complexity that needs to be properly accounted for in a SWT design [4, 6, 17, 90]. In this literature review, we identified only 16 studies that have taken into account in the analyses the clustering and time effects and the (potential) correlation between costs and outcomes by using appropriate mixed/multilevel methods, two using seemingly unrelated regression and eight a generic bootstrap. Unfortunately, generic bootstrap is not the most appropriate type of EE analyses as it might fail to accommodate clustering and the (potential) correlation between costs and outcomes as the two-stage bootstrap does.

Given the increasing popularity in the SWT design and to build upon the findings of this study, further research is required to simulate different SWT designs, sample sizes, clusters and the

confounder of time (with a common time-trend pattern for all clusters or site-specific time trends) in order to prescribe the potential statistical methods for EE to be used.

This study has some limitations. Firstly, the limited number of studies identified makes it difficult to summarise the different statistical methods used when conducting an EE alongside a SWT. Secondly, it is possible that some studies used appropriate methods, but failed to adequately document them. Finally, the lack of pertinent methodological papers and tutorials on the statistical methods available for EE in SWT might have contributed to the general uncertainty on the best approaches to employ that have been reflected in this review.

Conclusions

SWT designs are gaining popularity, but statistical methods for EE conducted alongside SWTs have not been sufficiently explored and used. The use of appropriate methods that account for time, clustering, and correlation between costs and outcomes is an important part of SWT health economics analysis that will benefit from an effort in communicating the methods available and performance.

Data Availability Statement

All data generated or analysed during this study are included in this published article (and its supplementary information files).

References

1. Hemming K, Taljaard M, McKenzie JE, Hooper R, Copas A, Thompson JA et al. Reporting of stepped wedge cluster randomised trials: extension of the CONSORT 2010 statement with explanation and elaboration. BMJ (Clinical research ed). 2018;363:k1614. doi:10.1136/bmj.k1614.
2. Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. Contemp Clin Trials. 2007;28(2):182-91. doi:10.1016/j.cct.2006.05.007.
3. Mdege ND, Man MS, Taylor Nee Brown CA, Torgerson DJ. Systematic review of stepped wedge cluster randomized trials shows that design is particularly used to evaluate interventions during routine implementation. Journal of clinical epidemiology. 2011;64(9):936-48. doi:10.1016/j.jclinepi.2010.12.003.
4. Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. BMJ (Clinical research ed). 2015;350:h391. doi:10.1136/bmj.h391.
5. Brown CA, Lilford RJ. The stepped wedge trial design: a systematic review. BMC medical research methodology. 2006;6:54. doi:10.1186/1471-2288-6-54.
6. Hemming K, Taljaard M. Reflection on modern methods: when is a stepped-wedge cluster randomized trial a good study design choice? International journal of epidemiology. 2020. doi:10.1093/ije/dyaa077.
7. Hooper R, Eldridge SM. Cutting edge or blunt instrument: how to decide if a stepped wedge design is right for you. BMJ quality & safety. 2020. doi:10.1136/bmjqs-2020-011620.
8. Prost A, Binik A, Abubakar I, Roy A, De Allegri M, Mouchoux C et al. Logistic, ethical, and political dimensions of stepped wedge trials: critical review and case studies. Trials. 2015;16:351. doi:10.1186/s13063-015-0837-4.
9. Eldridge S, Kerry S, Torgerson DJ. Bias in identifying and recruiting participants in cluster randomised trials: what can be done? BMJ (Clinical research ed). 2009;339:b4006. doi:10.1136/bmj.b4006.
10. Zhan Z, van den Heuvel ER, Doornbos PM, Burger H, Verberne CJ, Wiggers T et al. Strengths and weaknesses of a stepped wedge cluster randomized design: its application in a colorectal cancer follow-up study. Journal of clinical epidemiology. 2014;67(4):454-61. doi:10.1016/j.jclinepi.2013.10.018.
11. Bachmann MO, Fairall L, Clark A, Mugford M. Methods for analyzing cost effectiveness data from cluster randomized trials. Cost effectiveness and resource allocation : C/E. 2007;5:12. doi:10.1186/1478-7547-5-12.
12. Gomes M, Grieve R, Nixon R, Edmunds WJ. Statistical methods for cost-effectiveness analyses that use data from cluster randomized trials: a systematic review and checklist for critical appraisal. Medical decision making : an international journal of the Society for Medical Decision Making. 2012;32(1):209-20. doi:10.1177/0272989x11407341.
13. Grieve R, Nixon R, Thompson SG. Bayesian hierarchical models for cost-effectiveness analyses that use data from cluster randomized trials. Medical decision making : an international journal of the Society for Medical Decision Making. 2010;30(2):163-75. doi:10.1177/0272989x09341752.
14. Flynn TN, Peters TJ. Cluster randomized trials: another problem for cost-effectiveness ratios. International journal of technology assessment in health care. 2005;21(3):403-9. doi:10.1017/s0266462305050531.
15. Gomes M, Ng ES, Grieve R, Nixon R, Carpenter J, Thompson SG. Developing appropriate methods for cost-effectiveness analysis of cluster randomized trials. Medical decision making : an international journal of the Society for Medical Decision Making. 2012;32(2):350-61. doi:10.1177/0272989x11418372.

16. Hughes JP, Granston TS, Heagerty PJJCct. Current issues in the design and analysis of stepped wedge trials. 2015;45:55-60.
17. Copas AJ, Lewis JJ, Thompson JA, Davey C, Baio G, Hargreaves JR. Designing a stepped wedge trial: three main designs, carry-over effects and randomisation approaches. Trials. 2015;16:352. doi:10.1186/s13063-015-0842-7.
18. Moher D, Liberati A, Tetzlaff J, Altman DGJAoim. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. 2009;151(4):264-9.
19. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D et al. Consolidated health economic evaluation reporting standards (CHEERS)—explanation and elaboration: a report of the ISPOR health economic evaluation publication guidelines good reporting practices task force. 2013;16(2):231-50.
20. Badenbroek IFS, D. M. Nielen, M. M. Hollander, M. Kraaijenhagen, R. A. de Wit, G. A. Schellevis, F. G. de Wit, N. J. Design of the INTEGRATE study: effectiveness and cost-effectiveness of a cardiometabolic risk assessment and treatment program integrated in primary care. BMC family practice. 2014;15:90. doi:10.1186/1471-2296-15-90.
21. Bennett PND, R. M. Fraser, S. F. Haines, T. Barnard, R. Ockerby, C. Kent, B. The impact of an exercise physiologist coordinated resistance exercise program on the physical function of people receiving hemodialysis: a stepped wedge randomised control study. BMC nephrology. 2013;14:204. doi:10.1186/1471-2369-14-204.
22. Bernabe-Ortiz AD-C, F. Gilman, R. H. Cárdenas, M. K. Sacksteder, K. A. Miranda, J. J. Launching a salt substitute to reduce blood pressure at the population level: A cluster randomized stepped wedge trial in Peru. Trials. 2014;15(1). doi:10.1186/1745-6215-15-93.
23. Blackwood BA, A. Boyle, R. Clarke, M. Hemming, K. Jordan, J. Macrae, D. McAuley, D. F. McDowell, C. McIlmurray, L. Morris, K. P. Murray, M. Parslow, R. Peters, M. J. Tume, L. N. Walsh, T. Sedation and Weaning in Children (SANDWICH): Protocol for a cluster randomised stepped wedge trial. BMJ Open. 2019;9(11). doi:10.1136/bmjopen-2019-031630.
24. Bouwsma EVAB, J. E. Van Dongen, J. M. Brölmann, H. A. M. Anema, J. R. Huirne, J. A. F. Cost-effectiveness of an internet-based perioperative care programme to enhance postoperative recovery in gynaecological patients: Economic evaluation alongside a stepped-wedge cluster-randomised trial. BMJ Open. 2018;8(1). doi:10.1136/bmjopen-2017-017782.
25. Brady MCS, D. Weir, C. J. Chalmers, C. Sweeney, P. Donaldson, C. Barr, J. Barr, M. Pollock, A. McGowan, S. Bowers, N. Langhorne, P. Clinical and cost effectiveness of enhanced oral healthcare in stroke care settings (SOCLE II): a pilot, stepped wedge, cluster randomized, controlled trial protocol. International journal of stroke : official journal of the International Stroke Society. 2015;10(6):979-84. doi:10.1111/ijs.12530.
26. Brimblecombe J, Ferguson M, Liberato SC, Ball K, Moodie ML, Magnus A et al. Stores Healthy Options Project in Remote Indigenous Communities (SHOP@RIC): a protocol of a randomised trial promoting healthy food and beverage purchases through price discounts and in-store nutrition education. BMC public health. 2013;13:744. doi:10.1186/1471-2458-13-744.
27. Burchell ANA, V. G. Grewal, R. MacPherson, P. A. Rachlis, A. Walmsley, S. Mishra, S. Gardner, S. L. Raboud, J. Cooper, C. Gough, K. Rourke, S. B. Rousseau, R. Salit, I. Tan, D. H. S. Enhanced syphilis screening among HIV-positive men (ESSAHM): A study protocol for a clinic-randomized trial with stepped wedge design. Implementation Science. 2016;11(1). doi:10.1186/s13012-016-0371-0.
28. Dillon JFM, M. H. Robinson, E. M. Hapca, A. Rezaeihemami, M. Weatherburn, C. McIntyre, P. G. Bartlett, B. Donnan, P. T. Boyd, K. A. Dow, E. Intelligent liver function testing (iLFT): A trial of automated diagnosis and staging of liver disease in primary care. Journal of Hepatology. 2019;71(4):699-706. doi:10.1016/j.jhep.2019.05.033.
29. Eurich DT, Majumdar SR, Wozniak LA, Soprovich A, Meneen K, Johnson JA et al. Addressing the gaps in diabetes care in first nations communities with the reorganizing the approach to diabetes through the application of registries (RADAR): the project protocol. BMC health services research. 2017;17(1):117. doi:10.1186/s12913-017-2049-y.

30. Fotheringham JB, T. Dunn, L. Lee, S. Ariss, S. Young, T. Walters, S. J. Laboi, P. Henwood, A. Gair, R. Wilkie, M. Rationale and design for SHAREHD: a quality improvement collaborative to scale up Shared Haemodialysis Care for patients on centre based haemodialysis. BMC nephrology. 2017;18(1):335. doi:10.1186/s12882-017-0748-6.
31. Gerritsen DLS, M. Teerenstra, S. Leontjevas, R. Adang, E. M. Vernooij-Dassen, M. J. F. J. Derksen, E. Koopmans, R. T. C. M. Act In case of Depression: The evaluation of a care program to improve the detection and treatment of depression in nursing homes. Study Protocol. BMC Psychiatry. 2011;11. doi:10.1186/1471-244X-11-91.
32. Grossi U, Stevens N, McAlees E, Lacy-Colson J, Brown S, Dixon A et al. Stepped-wedge randomised trial of laparoscopic ventral mesh rectopexy in adults with chronic constipation: study protocol for a randomized controlled trial. 2018;19(1):90.
33. Harding KEW, J. J. Karimi, L. O'Reilly, M. Kent, B. Kotis, M. Leggat, S. G. Kearney, J. Taylor, N. F. Improving access for community health and sub-acute outpatient services: protocol for a stepped wedge cluster randomised controlled trial. BMC health services research. 2016;16(a):364. doi:10.1186/s12913-016-1611-3.
34. Hetherington SS, P. Henwood, T. Keogh, J. Gardiner, P. Tuckett, A. Rouse, K. Comans, T. Progressive Resistance Plus Balance Training for Older Australians Receiving In-Home Care Services: Cost-Effectiveness Analyses Alongside the Muscling Up Against Disability Stepped-Wedge Randomized Control Trial. Journal of aging and physical activity. 2019:1-8. doi:10.1123/japa.2019-0085.
35. James MTH, B. J. Tyrrell, B. D. Ma, B. Faris, P. Sajobi, T. T. Allen, D. W. Spertus, J. A. Wilton, S. B. Pannu, N. Klarenbach, S. W. Graham, M. M. Clinical Decision Support to Reduce Contrast-Induced Kidney Injury During Cardiac Catheterization: Design of a Randomized Stepped-Wedge Trial. The Canadian journal of cardiology. 2019;35(9):1124-33. doi:10.1016/j.cjca.2019.06.002.
36. Kim HP, Y. H. Jung, Y. I. Choi, H. Lee, S. Kim, G. S. Yang, D. W. Paik, M. C. Lee, T. J. Evaluation of a technology-enhanced integrated care model for frail older persons: Protocol of the SPEC study, a stepped-wedge cluster randomized trial in nursing homes. BMC Geriatrics. 2017;17(1). doi:10.1186/s12877-017-0459-7.
37. Kinchin IJ, S. Mann, J. Quigley, R. Harvey, D. Doran, C. M. Strivens, E. Efficacy and cost-effectiveness of a community-based model of care for older patients with complex needs: a study protocol for a multicentre randomised controlled trial using a stepped wedge cluster design. Trials. 2018;19(1):668. doi:10.1186/s13063-018-3038-0.
38. Kjeken IB, G. Bø, I. Dager, T. Dingsør, A. Hagfors, J. Hamnes, B. Eppeland, S. G. Fjerstad, E. Mowinckel, P. Nielsen, M. Rørstad, R. W. Sand-Svartrud, A. L. Slungaard, B. Wigers, S. H. Hagen, K. B. Evaluation of a structured goal planning and tailored follow-up programme in rehabilitation for patients with rheumatic diseases: Protocol for a pragmatic, stepped-wedge cluster randomized trial. BMC Musculoskeletal Disorders. 2014;15(1). doi:10.1186/1471-2474-15-153.
39. Kua CHY, C. Y. Y. Char, C. W. T. Tan, C. W. Y. Tan, P. C. Mak, V. S. Lee, S. W. H. Leong, I. Y. O. Nursing home team-care deprescribing study: A stepped-wedge randomised controlled trial protocol. BMJ Open. 2017;7(5). doi:10.1136/bmjopen-2016-015293.
40. Luckett TP, J. Agar, M. Lam, L. Davidson, P. M. McCaffrey, N. Boyle, F. Shaw, T. Currow, D. C. Read, A. Hosie, A. Lovell, M. Protocol for a phase III pragmatic stepped wedge cluster randomised controlled trial comparing the effectiveness and cost-effectiveness of screening and guidelines with, versus without, implementation strategies for improving pain in adults with cancer attending outpatient oncology and palliative care services: the Stop Cancer PAIN trial. BMC health services research. 2018;18(1):558. doi:10.1186/s12913-018-3318-0.
41. McCreight MSL-K, A. O'Donnell, C. I. Grunwald, G. K. Hebert, P. Gillette, M. Jneid, H. Parashar, A. Grossman, P. M. Helfrich, C. Mavromatis, K. Saket, G. Ho, P. M. Improving anti-platelet therapy adherence in the Veterans Health Administration: A randomized multi-site hybrid effectiveness-implementation study protocol. Contemporary Clinical Trials. 2019;77:104-10. doi:10.1016/j.cct.2018.12.005.

42. McNeely JT, A. B. Kunins, H. V. Shelley, D. Lee, J. D. Walley, A. Weinstein, Z. M. Billings, J. Davis, N. J. Marcello, R. K. Schackman, B. R. Barron, C. Bergmann, L. Study protocol for a pragmatic trial of the Consult for Addiction Treatment and Care in Hospitals (CATCH) model for engaging patients in opioid use disorder treatment. Addiction science & clinical practice. 2019;14(1):5. doi:10.1186/s13722-019-0135-7.
43. Miller P, Droste N, Egerton-Warburton D, Caldicott D, Fulde G, Ezard N et al. Driving change: A partnership study protocol using shared emergency department data to reduce alcohol-related harm. Emergency medicine Australasia : EMA. 2019;31(6):942-7. doi:10.1111/1742-6723.13266.
44. Muntinga MEH, E. O. Van Leeuwen, K. M. Van Hout, H. P. J. Twisk, J. W. R. Van Der Horst, H. E. Nijpels, G. Jansen, A. P. D. Implementing the chronic care model for frail older adults in the Netherlands: Study protocol of ACT (frail older adults: Care in transition). BMC Geriatrics. 2012;12. doi:10.1186/1471-2318-12-19.
45. Noordman BJW, B. P. L. Lagarde, S. M. Boonstra, J. J. Coene, P. P. L. O. Dekker, J. W. T. Doukas, M. van der Gaast, A. Heisterkamp, J. Kouwenhoven, E. A. Nieuwenhuijzen, G. A. P. Pierie, J. P. E. N. Rosman, C. van Sandick, J. W. van der Sangen, M. J. C. Sosef, M. N. Spaander, M. C. W. Valkema, R. van der Zaag, E. S. Steyerberg, E. W. van Lanschot, J. J. B. Biermann, K. Ista, E. Krak, N. C. Nuyttens, J. J. M. E. Polinder, S. Agool, A. Hoekstra, R. van der Linde, A. van Baarlen, J. Hendriksen, E. M. Bartels-Rutten, A. van Dieren, J. van Sandick, J. Snaebjornsson, P. Vegt, E. Voncken, F. E. M. Doornewaard, H. Erkelens, G. W. Madretsma, G. S. ten Broek, M. R. J. Dallinga, R. J. Dezentjé, V. O. de Krijger, R. R. Neelis, K. J. Quispel, R. Creemers, G. J. Schoon, E. J. Wyndaele, D. N. J. Buijsen, J. Riedl, R. G. Schreurs, W. M. J. Oostenbrug, L. E. Warmerdam, F. A. R. M. Slingerland, M. de Steur, W. O. Lips, I. M. Balink, H. Fiets, W. E. van der, K. Wolf, R. Oppedijk, V. Al Butaihi, I. Kliffen, M. Kuiper, E. M. M. Courrech, E. F. Janssen, M. J. R. Liedenbaum, M. H. van der Post, C. Radema, S. A. Rütten, H. Siersema, P. D. Beerepoot, L. V. Hazen, W. L. van Oord, J. C. Rozema, T. Vermeltfoort, I. A. C. van der Wurff, A. A. M. and on behalf of the, Sano-study group. Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: A stepped-wedge cluster randomised trial. BMC Cancer. 2018;18(1). doi:10.1186/s12885-018-4034-1.
46. Obermair AA, N. R. Graves, N. Gebski, V. Hanna, G. B. Coleman, M. G. Hughes, A. Janda, M. How to train practising gynaecologists in total laparoscopic hysterectomy: Protocol for the stepped-wedge IMAGINE trial. BMJ Open. 2019;9(5). doi:10.1136/bmjopen-2018-027155.
47. Richards-Belle AM, P. R. Wade, D. Brewin, C. R. Emerson, L. M. Grieve, R. Harrison, D. A. Harvey, S. Howell, D. Mythen, M. Sadique, Z. Smyth, D. Weinman, J. Welch, J. Rowan, K. M. Psychological Outcomes following a nurse-led Preventative Psychological Intervention for critically ill patients (POPPI): Protocol for a cluster-randomised clinical trial of a complex intervention. BMJ Open. 2018;8(2). doi:10.1136/bmjopen-2017-020908.
48. Rigal JCB, E. Lakhal, K. Riche, V. P. Durand-Zaleski, I. Rozec, B. Cost-effectiveness of point-of-care viscoelastic haemostatic assays in the management of bleeding during cardiac surgery: Protocol for a prospective multicentre pragmatic study with stepped-wedge cluster randomised controlled design and 1-year follow-up (the IMOTEC study). BMJ Open. 2019;9(11). doi:10.1136/bmjopen-2019-029751.
49. Rose OS, C. Czarnecki, K. Mennemann, H. S. Waltering, I. Hamacher, S. Felsch, M. Herich, L. Köberlein, J. Effect evaluation of an interprofessional medication therapy management approach for multimorbid patients in primary care: A cluster-randomized controlled trial in community care (WestGem study protocol). BMC Family Practice. 2015;16(1). doi:10.1186/s12875-015-0305-y.
50. Shawyer FE, J. C. Brophy, L. Bruxner, A. Fossey, E. Inder, B. Julian, J. Kakuma, R. Weller, P. Wilson-Evered, E. Edan, V. Slade, M. Meadows, G. N. The PULSAR Specialist Care protocol: a stepped-wedge cluster randomized control trial of a training intervention for community mental health teams in recovery-oriented practice. BMC Psychiatry. 2017;17(1):172. doi:10.1186/s12888-017-1321-3.
51. Stern AM, N. Paulden, M. Alibhai, S. Wong, J. Tomlinson, G. Brooker, A. S. Krahn, M. Zwarenstein, M. Pressure ulcer multidisciplinary teams via telemedicine: a pragmatic cluster randomized stepped wedge trial in long term care. BMC health services research. 2014;14:83. doi:10.1186/1472-6963-14-83.

52. Suman AS, F. G. van Dongen, J. M. Elders, P. J. M. Buchbinder, R. van Tulder, M. W. Anema, J. R. Effectiveness and cost-utility of a multifaceted eHealth strategy to improve back pain beliefs of patients with non-specific low back pain: a cluster randomised trial. BMJ Open. 2019;9(12):e030879. doi:10.1136/bmjopen-2019-030879.
53. van Holland BJR, M. F. Soer, R. Brouwer, S. de Boer, M. R. Effectiveness and Cost-benefit Evaluation of a Comprehensive Workers' Health Surveillance Program for Sustainable Employability of Meat Processing Workers. Journal of occupational rehabilitation. 2018;28(1):107-20. doi:10.1007/s10926-017-9699-9.
54. Van Leeuwen KMB, J. E. Jansen, A. P. D. Hoogendijk, E. O. Muntinga, M. E. Van Hout, H. P. J. Nijpels, G. Van Der Horst, H. E. Van Tulder, M. W. Cost-Effectiveness of a Chronic Care Model for Frail Older Adults in Primary Care: Economic Evaluation Alongside a Stepped-Wedge Cluster-Randomized Trial. Journal of the American Geriatrics Society. 2015;63(12):2494-504. doi:10.1111/jgs.13834.
55. Zwijsen SAB, J. E. Gerritsen, D. L. Pot, A. M. Hertogh, C. M. P. M. Smalbrugge, M. The cost-effectiveness of grip on challenging behaviour: An economic evaluation of a care programme for managing challenging behaviour. International Journal of Geriatric Psychiatry. 2016;31(6):567-74. doi:10.1002/gps.4360.
56. Al-Itejawi HHMVU-K, C. F. Van De Ven, P. M. Coupé, V. M. H. Vis, A. N. Nieuwenhuijzen, J. A. Van Moorselaar, J. A. Verdonck-De Leeuw, I. M. Effectiveness, cost-utility and implementation of a decision aid for patients with localised prostate cancer and their partners: Study protocol of a stepped-wedge cluster randomised controlled trial. BMJ Open. 2017;7(9). doi:10.1136/bmjopen-2016-015154.
57. Duhig KES, P. T. Myers, J. E. Bahl, R. Bambridge, G. Barnfield, S. Ficquet, J. Girling, J. C. Khalil, A. Shennan, A. H. Chappell, L. C. Hunter, R. M. Placental growth factor testing for suspected pre-eclampsia: a cost-effectiveness analysis. BJOG : an international journal of obstetrics and gynaecology. 2019;126(11):1390-8. doi:10.1111/1471-0528.15855.
58. Emond YEJJMC, H. Teerenstra, S. Bloo, G. J. A. Westert, G. P. Damen, J. Wolff, A. P. Wollersheim, H. C. Improving the implementation of perioperative safety guidelines using a multifaceted intervention approach: Protocol of the IMPROVE study, a stepped wedge cluster randomized trial. Implementation Science. 2015;10(1). doi:10.1186/s13012-014-0198-5.
59. Fadl HS, M. Montgomery, S. Magnuson, A. Schwarcz, E. Berntorp, K. Sengpiel, V. Storck-Lindholm, E. Strevens, H. Wikström, A. K. Brismar-Wendel, S. Persson, M. Jansson, S. Ahlsson, F. Ursing, C. Ryen, L. Petersson, K. Wennerholm, U. B. Hildén, K. Simmons, D. Changing diagnostic criteria for gestational diabetes in Sweden - A stepped wedge national cluster randomised controlled trial - The CDC4G study protocol. BMC Pregnancy and Childbirth. 2019;19(1). doi:10.1186/s12884-019-2547-5.
60. Haines TP, O'Brien L, Mitchell D, Bowles K-A, Haas R, Markham D et al. Study protocol for two randomized controlled trials examining the effectiveness and safety of current weekend allied health services and a new stakeholder-driven model for acute medical/surgical patients versus no weekend allied health services. 2015;16(1):133.
61. Hall LF, A. Mitchell, B. G. Barnett, A. G. Halton, K. Allen, M. Page, K. Gardner, A. Havers, S. Bailey, E. Dancer, S. J. Riley, T. V. Gericke, C. A. Paterson, D. L. Graves, N. Researching effective approaches to cleaning in hospitals: protocol of the REACH study, a multi-site stepped-wedge randomised trial. Implementation science : IS. 2016;11:44. doi:10.1186/s13012-016-0406-6.
62. Henrichs JV, V. Viester, L. Westerneng, M. Molewijk, B. Franx, A. van der Horst, H. Bosmans, J. E. de Jonge, A. Jellema, P. van Baar, A. L. Bais, J. Bonsel, G. J. van Dillen, J. van Duijnhoven, N. T. L. Grobman, W. A. Groen, H. Hukkelhoven, C. W. P. M. Klomp, T. Kok, M. de Kroon, M. L. Kruijt, M. Kwee, A. Ledda, S. Lafeber, H. N. van Lith, J. M. Mol, B. W. Nieuwenhuijze, M. Oei, G. Oudejans, C. Marieke Paarlberg, K. Pajkrt, E. Papageorghiou, A. T. Reddy, U. M. De Reu, P. A. O. M. Rijnders, M. de Roon-Immerzeel, A. Scheele, C. Scherjon, S. A. Snijders, R. Spaanderman, M. E. Teunissen, P. W. Torij, H. W. Vrijkotte, T. G. Twisk, J. Zeeman, K. C. Zhang, J. The, Iris Study Group. Effectiveness and cost-effectiveness of routine third trimester ultrasound screening for intrauterine growth restriction: Study protocol of a nationwide stepped wedge cluster-randomized trial in The Netherlands (The IRIS Study). BMC Pregnancy and Childbirth. 2016;16(1). doi:10.1186/s12884-016-1104-8.

63. Hill AMW, N. Etherton-Beer, C. McPhail, S. M. Ingram, K. Flicker, L. Haines, T. P. A stepped-wedge cluster randomised controlled trial for evaluating rates of falls among inpatients in aged care rehabilitation units receiving tailored multimedia education in addition to usual care: a trial protocol. BMJ Open. 2014;4(1):e004195. doi:10.1136/bmjopen-2013-004195.
64. Kc AB, A. Chaulagain, D. Brunell, O. Ewald, U. Gurung, A. Eriksson, L. Litorp, H. Wrammert, J. Gronqvist, E. Edin, P. A. Le Grange, C. Lamichhane, B. Shrestha, P. Pokharel, A. Pun, A. Singh, C. Malqvist, M. Scaling up quality improvement intervention for perinatal care in Nepal (NePeriQIP); study protocol of a cluster randomised trial. BMJ global health. 2017;2(3):e000497. doi:10.1136/bmjgh-2017-000497.
65. Mullane MJB, T. C. Cannon, J. W. Carapetis, J. R. Christophers, R. Coffin, J. Jones, M. A. Marsh, J. A. Mc Loughlin, F. O'Donnell, V. Pavlos, R. Smith, B. Steer, A. C. Tong, S. Y. C. Walker, R. Bowen, A. C. SToP (See, Treat, Prevent) skin sores and scabies trial: Study protocol for a cluster randomised, stepped-wedge trial for skin disease control in remote Western Australia. BMJ Open. 2019;9(9). doi:10.1136/bmjopen-2019-030635.
66. Osteras N, van Bodegom-Vos L, Dziedzic K, Moseng T, Aas E, Andreassen O et al. Implementing international osteoarthritis treatment guidelines in primary health care: study protocol for the SAMBA stepped wedge cluster randomized controlled trial. Implementation science : IS. 2015;10:165. doi:10.1186/s13012-015-0353-7.
67. Peden CJS, T. Martin, G. Kahan, B. C. Thomson, A. Everingham, K. Kocman, D. Lourtie, J. Drake, S. Girling, A. Lilford, R. Rivett, K. Wells, D. Mahajan, R. Holt, P. Yang, F. Walker, S. Richardson, G. Kerry, S. Anderson, I. Murray, D. Cromwell, D. Phull, M. Grocott, M. P. W. Bion, J. Pearse, R. M. the, Epoch trial group. Health Services and Delivery Research. A national quality improvement programme to improve survival after emergency abdominal surgery: the EPOCH stepped-wedge cluster RCT. Southampton (UK): NIHR Journals Library//Copyright (c) Queen's Printer and Controller of HMSO 2019. This work was produced by Peden et al. under the terms of a commissioning contract issued by the Secretary of State for Health and Social Care. This issue may be freely reproduced for the purposes of private research and study and extracts (or indeed, the full report) may be included in professional journals provided that suitable acknowledgement is made and the reproduction is not associated with any form of advertising. Applications for commercial reproduction should be addressed to: NIHR Journals Library, National Institute for Health Research, Evaluation, Trials and Studies Coordinating Centre, Alpha House, University of Southampton Science Park, Southampton SO16 7NS, UK.; 2019.
68. Poldervaart JMR, J. B. Backus, B. E. Koffijberg, H. Veldkamp, R. F. Ten Haaf, M. E. Appelman, Y. Mannaerts, H. F. J. Van Dantzig, J. M. Van Den Heuvel, M. El Farissi, M. Rensing, B. J. W. M. Ernst, N. M. S. K. J. Dekker, I. M. C. Den Hartog, F. R. Oosterhof, T. Lagerweij, G. R. Buijs, E. M. Van Hessen, M. W. J. Landman, M. A. J. Van Kimmenade, R. R. J. Cozijnsen, L. Bucx, J. J. J. Van Ofwegen-Hanekamp, C. E. E. Cramer, M. J. Six, A. J. Doevendans, P. A. Hoes, A. W. Effect of using the HEART score in patients with chest pain in the emergency department: A Stepped-wedge, cluster randomized trial. Annals of Internal Medicine. 2017;166(10):689-97. doi:10.7326/M16-1600.
69. Smit-Fun VMdK-dB, D. Posthuma, L. M. Stolze, A. Dirksen, C. D. Hollmann, M. W. Buhre, W. F. Boer, C. TRACE (Routine posTsuRgical Anesthesia visit to improve patient outComE): a prospective, multicenter, stepped-wedge, cluster-randomized interventional study. Trials. 2018;19(1):586. doi:10.1186/s13063-018-2952-5.
70. Straatman JC, M. A. Schreurs, W. H. H. Dwars, B. J. Cense, H. A. Rijna, H. Sonneveld, D. J. A. E. den Boer, F. C. de Lange- de Klerk, E. S. M. van der Peet, D. L. The PRECious trial PREdiction of Complications, a step-up approach, CRP first followed by CT-scan imaging to ensure quality control after major abdominal surgery: Study protocol for a stepped-wedge trial. Trials. 2015;16(1). doi:10.1186/s13063-015-0903-y.
71. Strijbos MJ, Steunenberg B, van der Mast RC, Inouye SK, Schuurmans MJ. Design and methods of the Hospital Elder Life Program (HELP), a multicomponent targeted intervention to prevent delirium in hospitalized older patients: efficacy and cost-effectiveness in Dutch health care. BMC geriatrics. 2013;13:78. doi:10.1186/1471-2318-13-78.

72. Wilson KSM, C. Bukusi, D. Inwani, I. Wagner, A. D. Moraa, H. Owens, T. Babigumira, J. B. Richardson, B. A. John-Stewart, G. C. Slyker, J. A. Wamalwa, D. C. Kohler, P. K. Simulated patient encounters to improve adolescent retention in HIV care in Kenya: study protocol of a stepped-wedge randomized controlled trial. Trials. 2017;18(1):619. doi:10.1186/s13063-017-2266-z.
73. Yates M, Watts JJ, Bail K, Mohebbi M, MacDermott S, Jebramek JC et al. Evaluating the Impact of the Dementia Care in Hospitals Program (DCHP) on Hospital-Acquired Complications: Study Protocol. International journal of environmental research and public health. 2018;15(9). doi:10.3390/ijerph15091878.
74. Ayorinde JOOS, D. M. Pankhurst, L. Laing, E. Deary, A. J. Hemming, K. Wilson, E. C. F. Bardsley, V. Neil, D. A. Pettigrew, G. J. PreImplantation Trial of Histopathology in renal Allografts (PITHIA): A steppedwedge cluster randomised controlled trial protocol. BMJ Open. 2019;9(1). doi:10.1136/bmjopen-2018-026166.
75. Battle CA, Z. Hutchings, H. A. O'Neill, C. Groves, S. Watkins, A. Lecky, F. E. Jones, S. Gagg, J. Body, R. Evans, P. A. Protocol for a multicentre randomised feasibility STUdy evaluating the impact of a prognostic model for Management of BLunt chest wall trauma patients: STUMBL trial. BMJ Open. 2017;7(7):e015972. doi:10.1136/bmjopen-2017-015972.
76. Blanchet KL, J. J. Pozo-Martin, F. Satouro, A. Somda, S. Ilboudo, P. Sarrassat, S. Cousens, S. A mixed methods protocol to evaluate the effect and cost-effectiveness of an Integrated electronic Diagnosis Approach (IeDA) for the management of childhood illnesses at primary health facilities in Burkina Faso. Implementation science : IS. 2016;11(1):111. doi:10.1186/s13012-016-0476-5.
77. Cavallaro FL, Duclos D, Baggaley RF, Penn-Kekana L, Goodman C, Vahanian A et al. Taking stock: protocol for evaluating a family planning supply chain intervention in Senegal. Reproductive health. 2016;13:45. doi:10.1186/s12978-016-0163-7.
78. Cunnama LA, E. J. Myer, L. Gachuhi, A. Dlamini, N. Hlophe, T. Kikuvi, J. Langwenya, N. Mthethwa, S. Mudonhi, D. Nhlabatsi, B. Nuwagaba-Biribonwoha, H. Okello, V. Sahabo, R. Zerbe, A. Sinanovic, E. Cost and cost-effectiveness of transitioning to universal initiation of lifelong antiretroviral therapy for all HIV-positive pregnant and breastfeeding women in Swaziland. Tropical medicine & international health : TM & IH. 2018;23(9):950-9. doi:10.1111/tmi.13121.
79. D'Onofrio GE, E. J. Hawk, K. F. Pantalon, M. V. Chawarski, M. C. Owens, P. H. Martel, S. H. VanVeldhuisen, P. Oden, N. Murphy, S. M. Huntley, K. O'Connor, P. G. Fiellin, D. A. Implementation facilitation to promote emergency department-initiated buprenorphine for opioid use disorder: protocol for a hybrid type III effectiveness-implementation study (Project ED HEALTH). Implementation science : IS. 2019;14(1):48. doi:10.1186/s13012-019-0891-5.
80. Mitchell BGF, O. Cheng, A. C. Gregory, V. Koerner, J. Collignon, P. Gardner, A. Graves, N. Chlorhexidine versus saline in reducing the risk of catheter associated urinary tract infection: A cost-effectiveness analysis. International journal of nursing studies. 2019;97:1-6. doi:10.1016/j.ijnurstu.2019.04.003.
81. Snooks HB-J, K. Burge-Jones, D. Dale, J. Davies, J. Evans, B. A. Farr, A. Fitzsimmons, D. Heaven, M. Howson, H. Hutchings, H. John, G. Kingston, M. Lewis, L. Phillips, C. Porter, A. Sewell, B. Warm, D. Watkins, A. Whitman, S. Williams, V. Russell, I. Effects and costs of implementing predictive risk stratification in primary care: A randomised stepped wedge trial. BMJ Quality and Safety. 2019;28(9):697-705. doi:10.1136/bmjqs-2018-007976.
82. Ashish KCB, A. Chaulagain, D. Brunell, O. Ewald, U. Gurung, A. Eriksson, L. Litorp, H. Wrammert, J. Grönqvist, E. Edin, P. A. Grange, C. L. Lamichhane, B. Shrestha, P. Pokharel, A. Pun, A. Singh, C. Målqvist, M. Scaling up quality improvement intervention for perinatal care in Nepal (NePeriQIP); Study protocol of a cluster randomised trial. BMJ Global Health. 2017;2(3). doi:10.1136/bmjgh-2017-000497.
83. Dreischulte TG, A. Donnan, P. McCowan, C. Davey, P. Petrie, D. Treweek, S. Guthrie, B. A cluster randomised stepped wedge trial to evaluate the effectiveness of a multifaceted information technology-based intervention in reducing high-risk prescribing of non-steroidal anti-inflammatory

drugs and antiplatelets in primary medical care: the DQIP study protocol. Implementation science : IS. 2012;7:24. doi:10.1186/1748-5908-7-24.
84. Nathan HLD, K. Vousden, N. Lawley, E. Seed, P. T. Sandall, J. Bellad, M. B. Brown, A. C. Chappell, L. C. Goudar, S. S. Gidiri, M. F. Shennan, A. H. Hezelgrave, N. L. Charantimath, U. Karadiguddi, C. C. Mastiholi, S. S. Mungarwadi, G. M. Surur, F. Yadeta, L. Guchale, Y. Mambo, V. Chinkoyo, S. Musonda, T. Jere, C. Vwalika, B. Kopeka, M. Chima, M. Miti, J. Best, R. Clarke, M. Kamara, J. Conteh, J. Sandi, P. Sesay, M. Momodou, F. Wandabwa, J. Ditai, J. Odeke, N. M. Nakimuli, A. Byamugisha, J. Namakula, D. Kalyowa, N. Birungi, D. Nakirijja, E. Hill, C. Greene, G. Vixama, A. Toussaint, P. Makonyola, G. Bukani, D. Kachinjika, M. Makwakwa, J. and the, Cradle-Trial Collaboration Group. Evaluation of a novel device for the management of high blood pressure and shock in pregnancy in low-resource settings: Study protocol for a stepped-wedge cluster-randomised controlled trial (CRADLE-3 trial). Trials. 2018;19(1). doi:10.1186/s13063-018-2581-z.
85. Sánchez AT, C. Deeken, F. Wagner, S. Klöppel, S. Kentischer, F. Von Arnim, C. A. F. Denkinger, M. Conzelmann, L. O. Biermann-Stallwitz, J. Joos, S. Sturm, H. Metz, B. Auer, R. Skrobik, Y. Eschweiler, G. W. Rapp, M. A. Metzger, F. Straub, A. Krüger, T. Bausenhart, F. Renz, P. Walther, A. Bruns, C. Spank, J. Sabbah, P. Häusler, A. Förstner, B. Schulze, S. Maurer, C. Martin, M. Heimbach, B. Voigt-Radloff, S. Reichel, H. Liebold, A. Küster, O. Brefka, S. Kirschner, S. Stober, N. Mehlhorn, U. Wasem, J. Neumann, A. Patient safety, cost-effectiveness, and quality of life: Reduction of delirium risk and postoperative cognitive dysfunction after elective procedures in older adults - Study protocol for a stepped-wedge cluster randomized trial (PAWEL Study). Trials. 2019;20(1). doi:10.1186/s13063-018-3148-8.
86. Sweeney RM, M. Nguyen, P. Fraser, P. Bolton, K. Brown, A. Marks, J. Crooks, N. Strugnell, C. Bell, C. Millar, L. Orellana, L. Allender, S. Protocol for an economic evaluation of WHO STOPS childhood obesity stepped-wedge cluster randomised controlled trial. BMJ Open. 2018;8(5):e020551. doi:10.1136/bmjopen-2017-020551.
87. Walsh FJB, T. Delva, W. Fleming, Y. Khumalo, G. Lejeune, C. L. Mazibuko, S. Mlambo, C. K. Reis, R. Spiegelman, D. Zwane, M. Okello, V. Impact of early initiation versus national standard of care of antiretroviral therapy in Swaziland's public sector health system: Study protocol for a stepped-wedge randomized trial. Trials. 2017;18(1). doi:10.1186/s13063-017-2128-8.
88. Yoo BKS, S. J. Humiston, S. G. Rand, C. M. Goldstein, N. P. N. Albertin, C. S. Concannon, C. Szilagyi, P. G. Cost effectiveness of school-located influenza vaccination programs for elementary and secondary school children. BMC health services research. 2019;19(1):407. doi:10.1186/s12913-019-4228-5.
89. El Alili M, van Dongen JM, Goldfeld KS, Heymans MW, van Tulder MW, Bosmans JE. Taking the Analysis of Trial-Based Economic Evaluations to the Next Level: The Importance of Accounting for Clustering. PharmacoEconomics. 2020. doi:10.1007/s40273-020-00946-y.
90. Hemming K, Taljaard M, Forbes A. Analysis of cluster randomised stepped wedge trials with repeated cross-sectional samples. Trials. 2017;18(1):101. doi:10.1186/s13063-017-1833-7.

Declarations

Funding: Thomas Lung is supported by an NHMRC Early Career Fellowship (APP1141392) and a National Heart Foundation Postdoctoral Fellowship (award ID 101956). Lei Si is funded by a National Health and Medical Research Council Early Career Fellowship (Grant number GNT1139826).

Conflict of interest: The authors have no conflict of interest that are directly relevant to the content of this article.

Acknowledgements: The authors thank Katrina Birrell for initiating the search strategy and identifying key search terms.

Authors' Contributions: TL, LS and GLDT contributed to the study design: title, abstract, and full-text reviews: and data extraction. Data were analysed by TL and LS. The final manuscript was drafted by TL, RH and GLDT. All authors read and approved the manuscript.