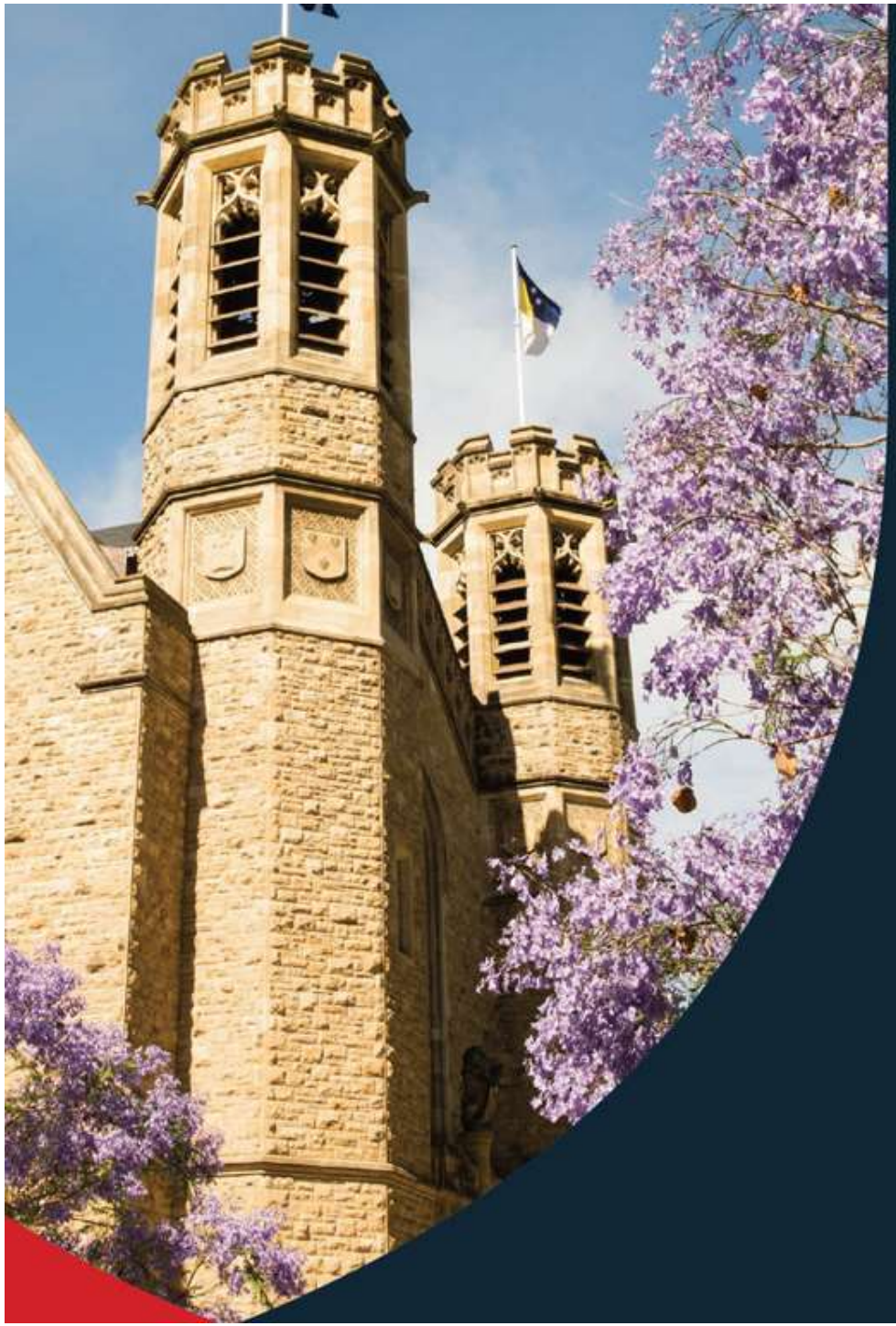

Clinical Trial Designs

Danny Liew

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Acknowledgement of Country

I acknowledge and pay my respects to the Kaurna people, the traditional custodians whose ancestral lands we gather on.

I acknowledge the deep feelings of attachment and relationship of the Kaurna people to country and I respect and value their past, present and ongoing connection to the land and cultural beliefs.

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CALHN Research Exchange

14-18 October 2024

CALHN Research Exchange - Plenary Lecture

Mon, Oct 14 • 1:00 PM

Royal Adelaide Hospital

Free

CALHN Research Exchange - Skills Workshop

Tue, Oct 15 • 9:00 AM

Royal Adelaide Hospital

Free

CALHN Research Exchange - Poster Pitches

Tue, Oct 15 • 11:00 AM + 1 more

Royal Adelaide Hospital

Free

2024 Debate & Research Awards

Wed, Oct 16 • 4:00 PM

Auditorium, SAHMRI (South Australian Health and Medical...

Free

TQEH Research Expo - Scientific Presentations

Thu, Oct 17 • 1:00 PM

Basil Hetzel Institute (Seminar Room)

Free

TQEH Research Expo - Scientific Presentations, Plenary Lecture & Awards

Fri, Oct 18 • 8:15 AM

Basil Hetzel Institute (Seminar Room)

Free

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https://www.eventbrite.com/cc/calhn-research-exchange-2024-3628029

Overview

- registry-based clinical trials
- equivalence and non-inferiority trials
- cross-over studies
- factorial studies
- cluster trials
- stepped-wedge studies
- propensity-score analysis

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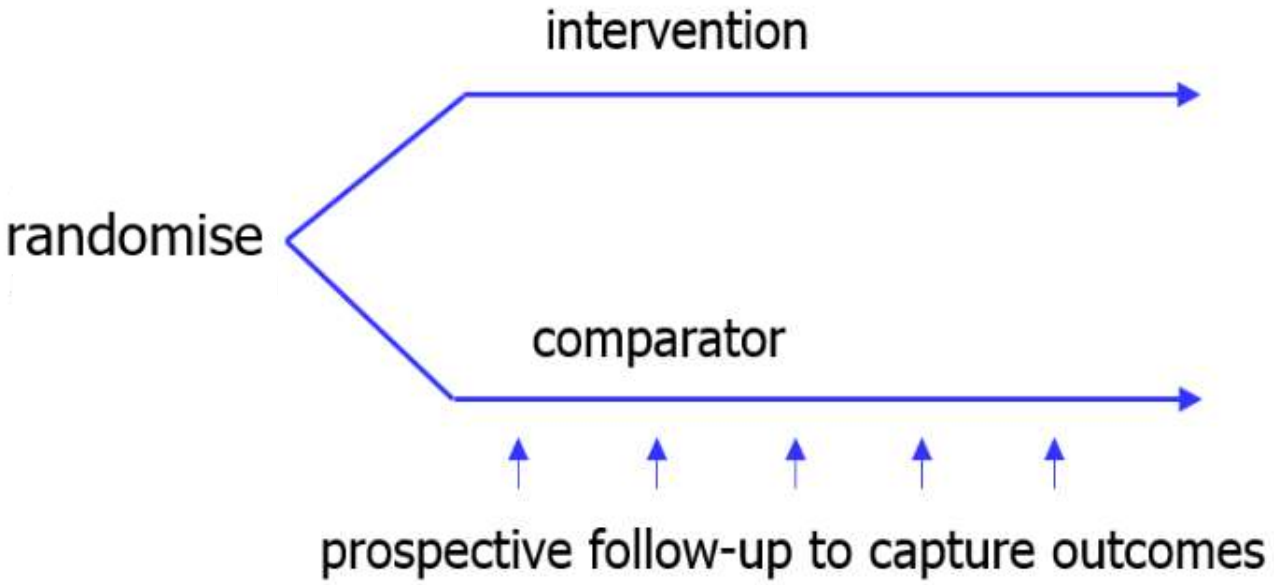
Classic Parallel Design



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Registry-Based Clinical Trials

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Registry-Based Clinical Trials

- same design as 'typical' clinical trials
- nested within clinical registries
- 2 major advantages:
  i. more representative subjects
  ii. follow-up occurs (mostly) as usual function of registry

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bivalirudin versus Heparin Monotherapy in Myocardial Infarction

METHODS

In this multicenter, randomized, registry-based, open-label clinical trial, we enrolled patients with either ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) who were undergoing PCI and receiving treatment with a potent $P2Y_{12}$ inhibitor (ticagrelor, prasugrel, or cangrelor) without the planned use of glycoprotein IIb/IIIa inhibitors. The patients were randomly assigned to receive bivalirudin or heparin during PCI, which was performed predominantly with the use of radial-artery access. The primary end point was a composite of death from any cause, myocardial infarction, or major bleeding during 180 days of follow-up.

*SWEDEHEART: Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies

N Engl J Med 2017;377:1132-42.

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Equivalence and Non-Inferiority Trials

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Equivalence and Non-Inferiority Trials

- comparison of new intervention against current best practice (usually active)
- to demonstrate:
  - *equivalence* - not more *and* not less efficacious
  - *non-inferiority* - not less efficacious

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Rationale

- advantage(s) of new intervention in terms of factors other than efficacy

  eg, adverse effects, costs, pharmacokinetics

- to join an existing market

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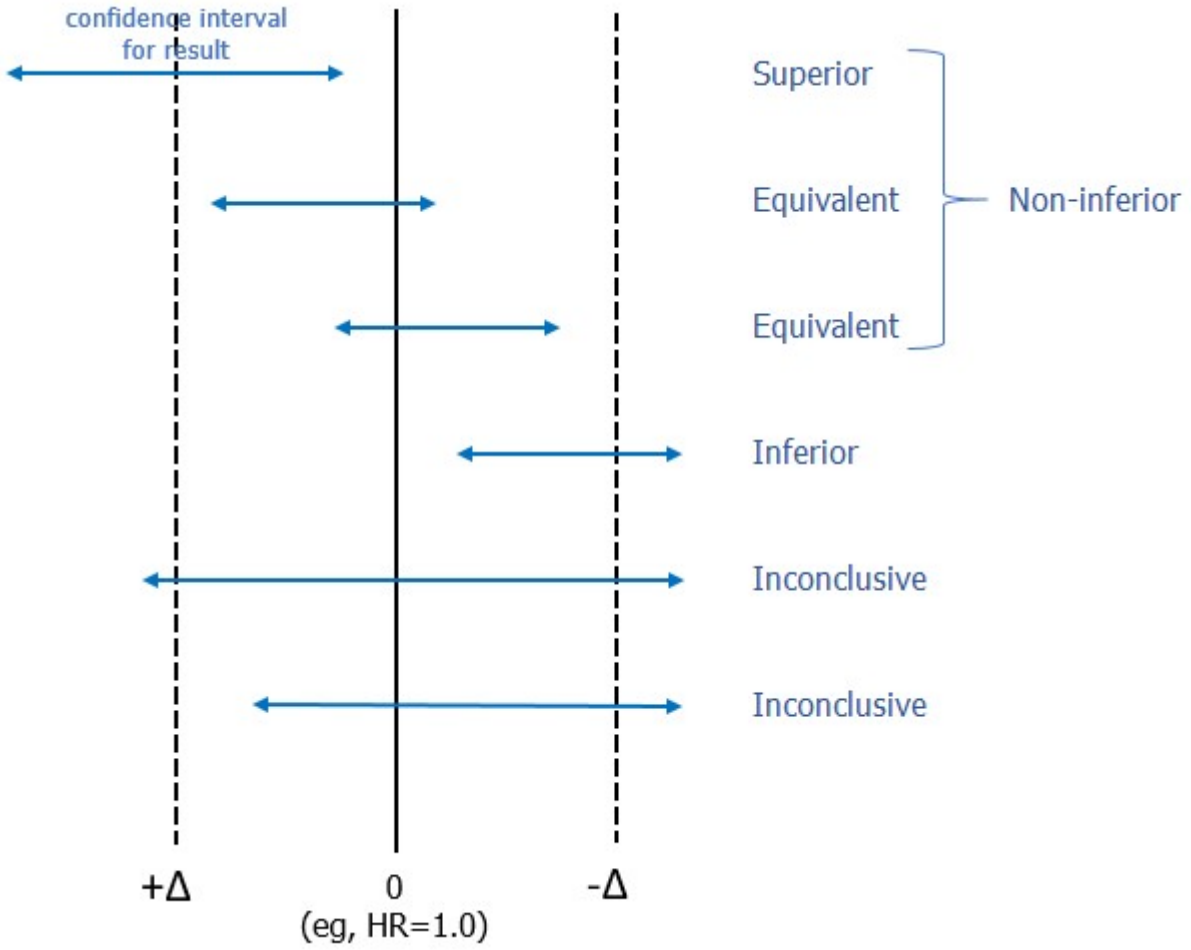

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Sample Size of Different Trials

ascending order (in general):

- placebo-controlled superiority trial
- active-controlled superiority trial

  $\approx$

  non-inferiority trial
- equivalence trial

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban versus Warfarin in Patients with Atrial Fibrillation

METHODS

In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

N Engl J Med 2011; 365:981-92

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Cross-Over Studies

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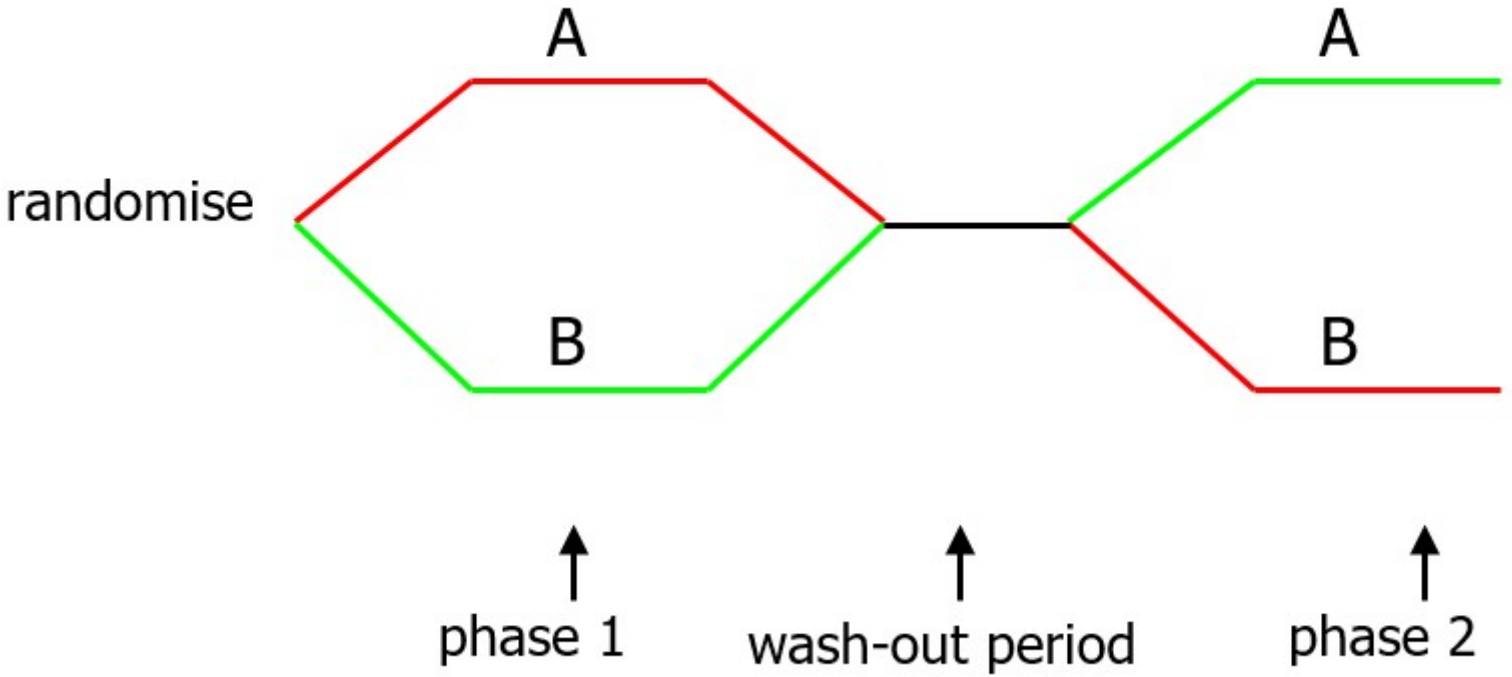
Cross-Over Studies



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Cross-Over Studies

- subjects assigned to one group first, then cross-over into the other
- subjects serve as own controls
- main measure: within-subject differences

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Cross-Over Studies

- less subjects required
- effects of interventions have to be short-term and reversible
- need for stable underlying condition

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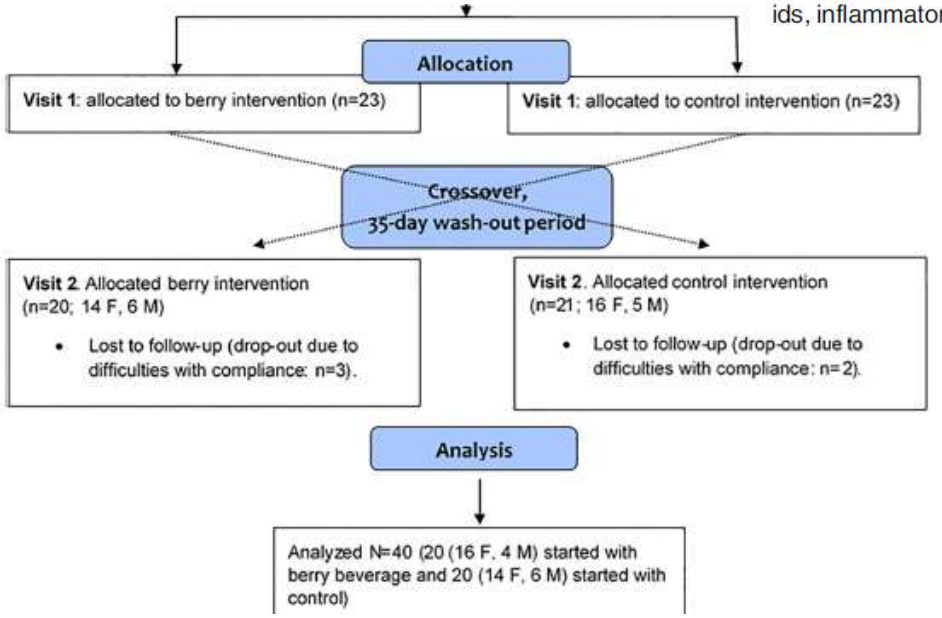
RESEARCH ARTICLE

Effects of a mixed berry beverage on cognitive functions and cardiometabolic risk markers; A randomized cross-over study in healthy older adults

Anne Nilsson[1,2]*, Ilkka Salo[3], Merichel Plaza[4¤], Inger Björck[1]

Methods

Forty healthy subjects between 50–70 years old were provided a berry beverage based on a mixture of berries (150g blueberries, 50g blackcurrant, 50g elderberry, 50g lingonberries, 50g strawberry, and 100g tomatoes) or a control beverage, daily during 5 weeks in a randomized crossover design. The control beverage (water based) was matched with respect to monosaccharides, pH, and volume. Cognitive tests included tests of working memory capacity, selective attention, and psychomotor reaction time. Cardiometabolic test variables investigated were blood pressure, fasting blood concentrations of glucose, insulin, blood lipids, inflammatory markers, and markers of oxidative stress.



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PLoS ONE 12(11): e0188173. https://doi.org/10.1371/journal.pone.0188173

Factorial Studies

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Factorial Studies

- subjects assigned to >1 set of interventions

  simultaneously in a single trial

- simultaneous testing of >1 different interventions

- multiple trials in one

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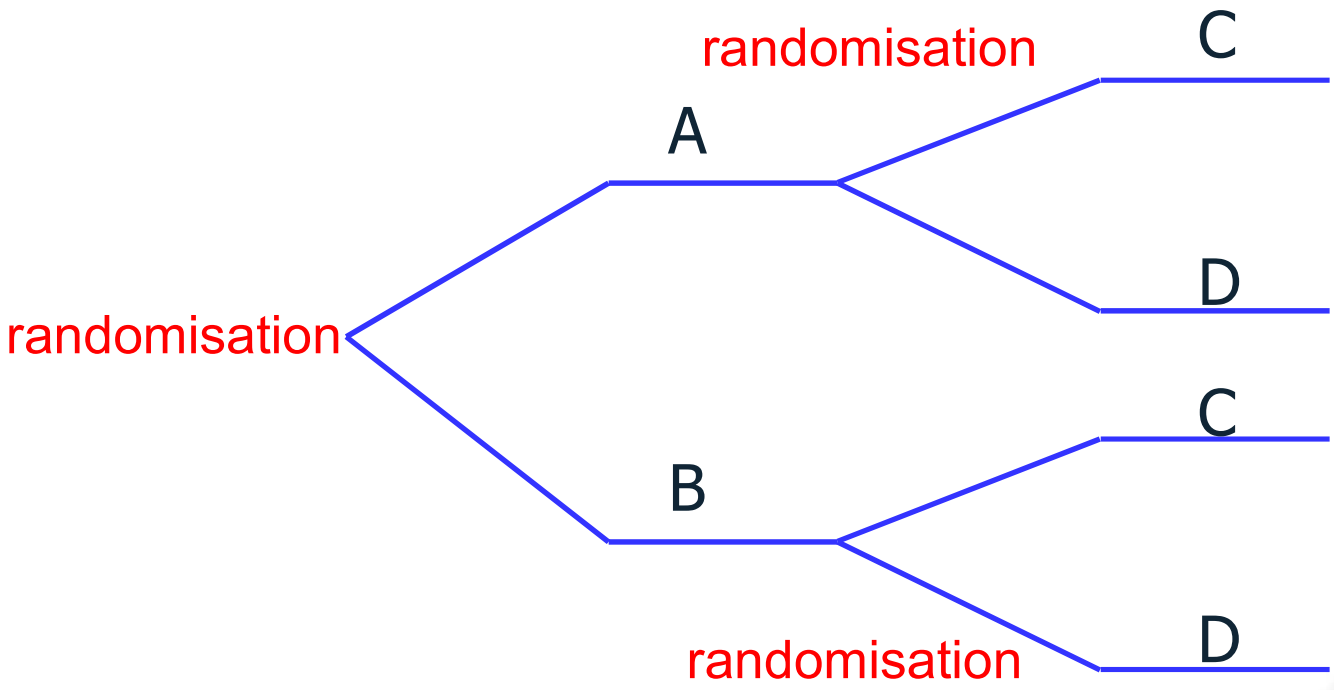
Factorial Studies



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Factorial Studies

- efficient use of resources and subjects
- 2 trials simultaneously, not 1 trial of 4 interventions

  ie, A vs B and C vs D (not AC vs AD vs BC vs BD)
- need for independent effects of the 2 sets of

  interventions (ie, no interactions)

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The NEW ENGLAND JOURNAL of MEDICINE

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

S. Yusuf, J. Bosch, G. Dagenais, J. Zhu, D. Xavier, L. Liu, P. Pais, P. López-Jaramillo, L.A. Leiter, A. Dans, A. Avezum, L.S. Piegas, A. Parkhomenko, K. Keltai, M. Keltai, K. Sliwa, R.J.G. Peters, C. Held, I. Chazova, K. Yusoff B.S. Lewis, P. Jansky, K. Khunti, W.D. Toff, C.M. Reid, J. Varigos, G. Sanchez-Vallejo, R. McKelvie, J. Pogue,* H. Jung, P. Gao, R. Diaz, and E. Lonn, for the HOPE-3 Investigators†

Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Eva M. Lonn, M.D., Jackie Bosch, Ph.D., Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Lisheng Liu, M.D., Prem Pais, M.D., Rafael Diaz, M.D., Denis Xavier, M.D., Karen Sliwa, M.D., Ph.D., Antonio Dans, M.D., Alvaro Avezum, M.D., Ph.D., Leopoldo S. Piegas, M.D., Ph.D., Katalin Keltai, M.D., Ph.D., Matyas Keltai, M.D., Ph.D., Irina Chazova, M.D., Ph.D., Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D., Basil S. Lewis, M.D., Petr Jansky, M.D., Alexander Parkhomenko, M.D., Ph.D., Kamlesh Khunti, M.D., Ph.D., William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc., Lawrence A. Leiter, M.D., Dora I. Molina, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,* Joanne Wilkinson, B.A., Hyejung Jung, M.Sc., Gilles Dagenais, M.D., and Salim Yusuf, M.B., B.S., D.Phil., for the HOPE-3 Investigators†

	Candesartan 16mg / HCTZ 12.5mg n = 6356	Placebo n= 6349
Rosuvastatin 10mg n = 6361	Rosuva + Cand/HCTZ n = 3180	Rosuva + PBO n = 3181
Placebo n = 6349	Cand/HCTZ + PBO n = 3176	PBO + PBO n = 3168

New Engl J Med 374;21

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Cluster Trials

Cluster Trials

- randomise groups instead of individuals

  eg - teams, clinics, wards

- minimise within-group 'contamination'

- challenge: sufficient groups, sufficiently similar

- sample size / power still based on individuals, but accounts for 'clustering'

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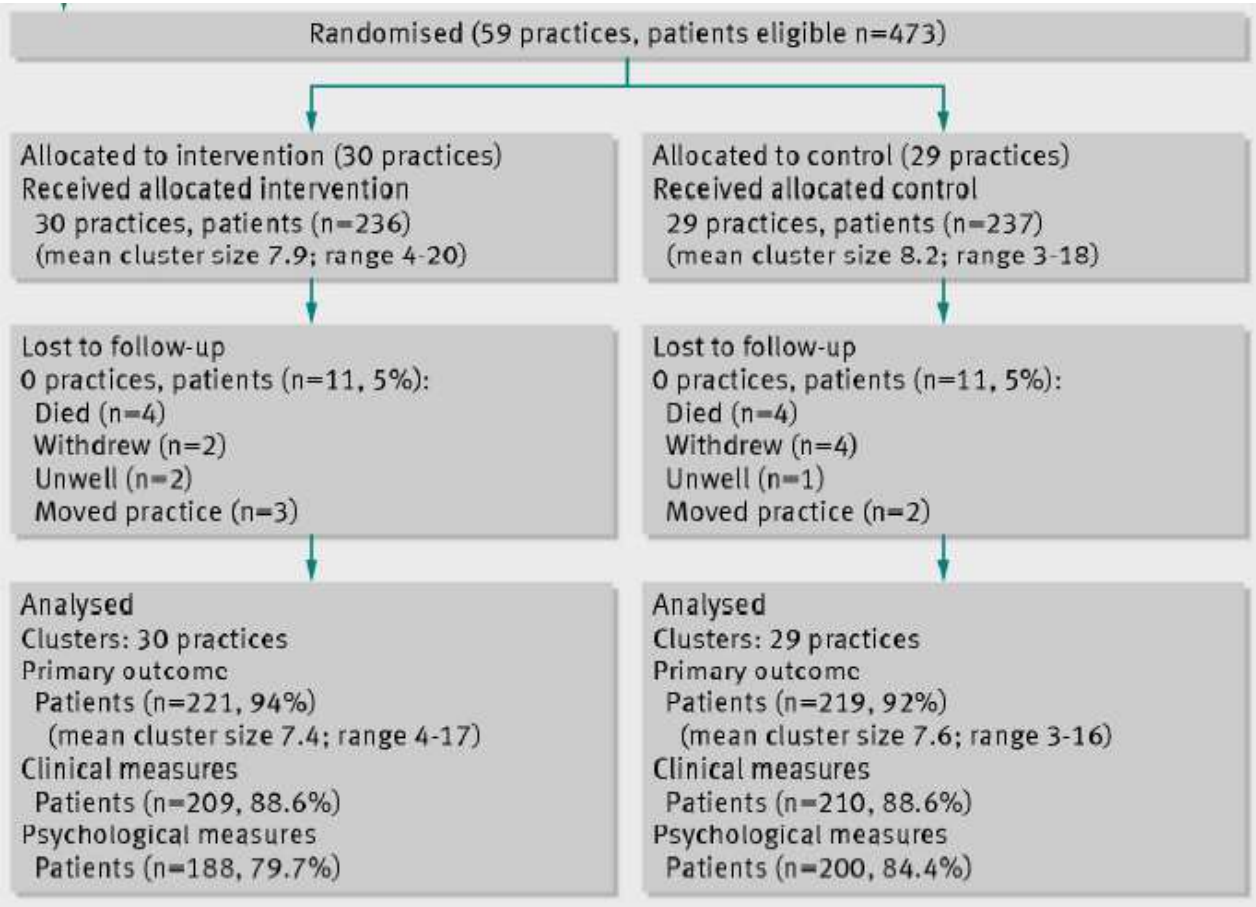
BMJ

Effectiveness of general practice based, practice nurse led telephone coaching on glycaemic control of type 2 diabetes: the Patient Engagement And Coaching for Health (PEACH) pragmatic cluster randomised controlled trial

OPEN ACCESS



Primary end point: mean absolute change in HbA1c between baseline and 18 months

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BMJ 2013;347:f5272 doi: 10.1136/bmj.f5272

Stepped-Wedge Studies

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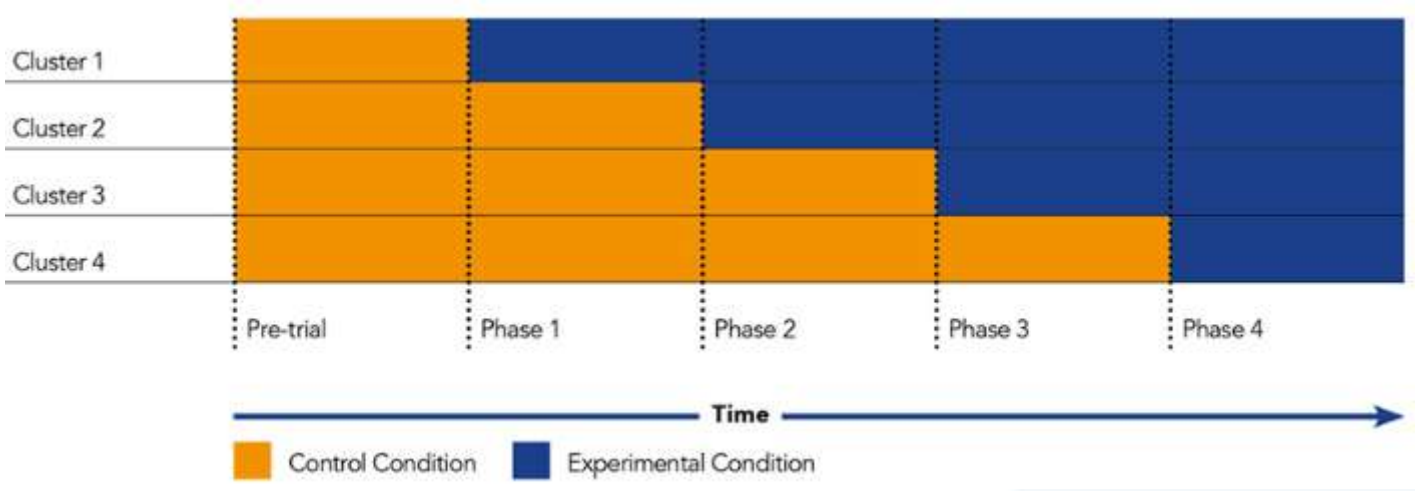
Stepped-Wedge Studies

- cluster trials with sequential one-way cross-over
- sequence of cross-over is random
- comparison: intervention vs control across groups



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https://researchoutreach.org/articles/stepped-wedge-cluster-randomised-trial-good-design-choice/

Awareness of fetal movements and care package to reduce fetal mortality (AFFIRM): a stepped wedge, cluster-randomised trial

Jane E Norman, Alexander E P Heazell, Aryelly Rodriguez, Christopher J Weir, Sarah J E Stock, Catherine J Calderwood, Sarah Cunningham Burley, J Frederik Frøen, Michael Geary, Fionnuala Breathnach, Alyson Hunter, Fionnuala M McAuliffe, Mary F Higgins, Edile Murdoch, Mary Ross-Davie, Janet Scott, Sonia Whyte, for the AFFIRM investigators

Background 2·6 million pregnancies were estimated to have ended in stillbirth in 2015. The aim of the AFFIRM study was to test the hypothesis that introduction of a reduced fetal movement (RFM), care package for pregnant women and clinicians that increased women's awareness of the need for prompt reporting of RFM and that standardised management, including timely delivery, would alter the incidence of stillbirth.

Methods This stepped wedge, cluster-randomised trial was done in the UK and Ireland. Participating maternity hospitals were grouped and randomised, using a computer-generated allocation scheme, to one of nine intervention implementation dates (at 3 month intervals). This date was concealed from clusters and the trial team until 3 months before the implementation date. Each participating hospital had three observation periods: a control period from Jan 1, 2014, until randomised date of intervention initiation; a washout period from the implementation date and for 2 months; and the intervention period from the end of the washout period until Dec 31, 2016. Treatment allocation was not concealed from participating women and caregivers. Data were derived from observational maternity data. The primary outcome was incidence of stillbirth. The primary analysis was done according to the intention-to-treat principle, with births analysed according to whether they took place during the control or intervention periods, irrespective of whether the intervention had been implemented as planned. This study is registered with ClinicalTrials.gov, number NCT01777022.

Findings 37 hospitals were enrolled in the study. Four hospitals declined participation, and 33 hospitals were randomly assigned to an intervention implementation date. Between Jan 1, 2014, and Dec, 31, 2016, data were collected from 409 175 pregnancies (157 692 deliveries during the control period, 23 623 deliveries in the washout period, and 227 860 deliveries in the intervention period). The incidence of stillbirth was 4·40 per 1000 births during the control period and 4·06 per 1000 births in the intervention period (adjusted odds ratio [aOR] 0·90, 95% CI 0·75–1·07; p=0·23).

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Lancet 2018; 392: 1629-38

Propensity Score Analysis

Propensity Score Analysis

- undertaken in observational studies - ie, no randomisation
- allows for comparison of 2 (or more) groups
- groups appear like they were randomised
- core component of *real-world evidence*

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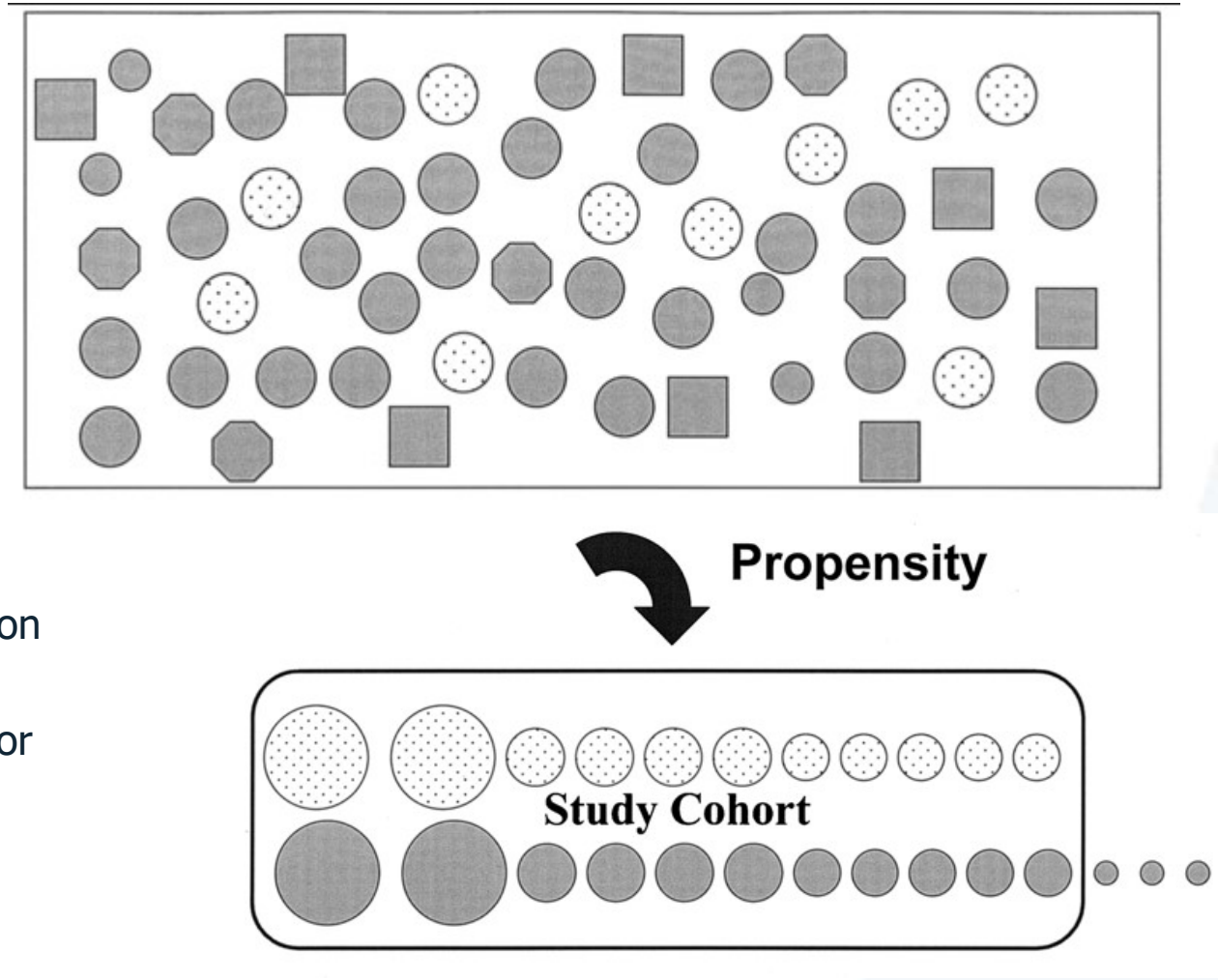
Propensity Score Analysis



intervention

comparator

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Propensity Score Analysis

advantages

- real-world representativeness
- relatively easy and inexpensive

disadvantages

- not equivalent to randomisation
- residual confounding
- need for large sample sizes

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Lower Risk of Heart Failure and Death in Patients Initiated on Sodium-Glucose Cotransporter-2 Inhibitors Versus Other Glucose-Lowering Drugs

The CVD-REAL Study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors)

METHODS: Data were collected via medical claims, primary care/hospital records, and national registries from the United States, Norway, Denmark, Sweden, Germany, and the United Kingdom. Propensity score for SGLT-2i initiation was used to match treatment groups. Hazard ratios for HHF, death, and their combination were estimated by country and pooled to determine weighted effect size. Death data were not available for Germany.

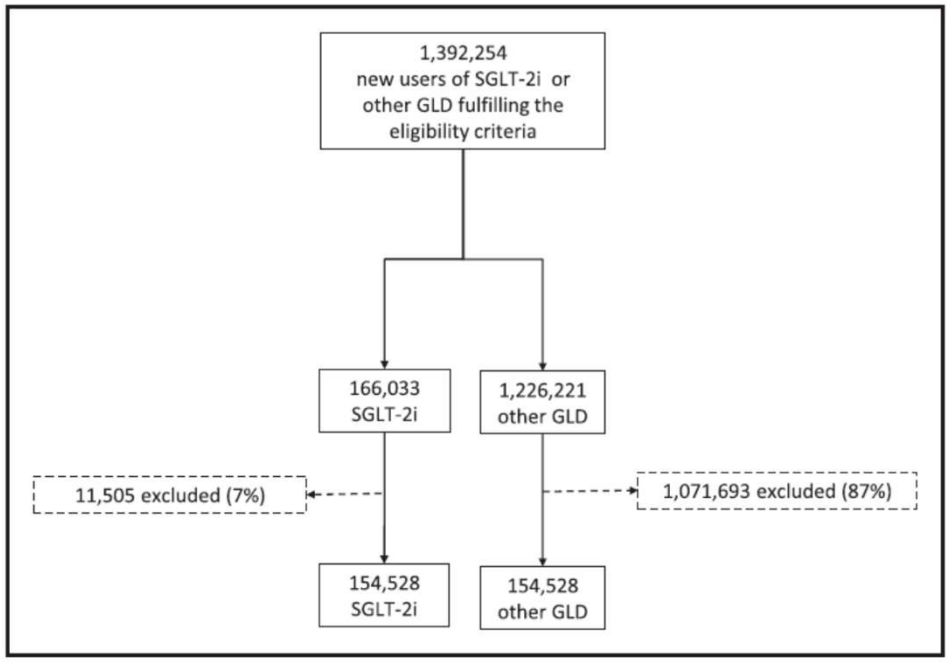

Figure 1. Patient flow chart for all countries/databases combined.

Circulation. 2017;136:249-259.

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  https://www.fda.gov/media/120721/download

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