

2nd KCE TRIALS SYMPOSIUM
28th November 2017

Introduction to Pragmatic Trials Including Cluster Randomised Trials and Stepped Wedge Designs

Sandra Eldridge

Pragmatic Clinical Trials Unit
Centre for Primary Care and Public Health



Outline

Pragmatic trials, what, when, and how?

Cluster randomised trials

Stepped wedge designs

Definitions

- Schwartz and Lellouch (J. Chron. Dis. 1967;20:637-48)
 - Pragmatic trials = to help choose between care options
 - Explanatory trials = to test causal research hypotheses
- Roland and Torgerson (*BMJ* 1998;316:285)
 - Pragmatic trials measure **effectiveness**—the benefit the treatment produces in routine clinical practice
 - Explanatory trials generally measure **efficacy**—the benefit a treatment produces under ideal conditions

EXPLANATORY

PRAGMATIC

How pragmatic/how explanatory?

RESEARCH METHODS & REPORTING



The PRECIS-2 tool: designing trials that are fit for purpose

Kirsty Loudon,¹ Shaun Treweek,¹ Frank Sullivan,² Peter Donnan,³ Kevin E Thorpe,⁴ Merrick Zwarenstein⁵

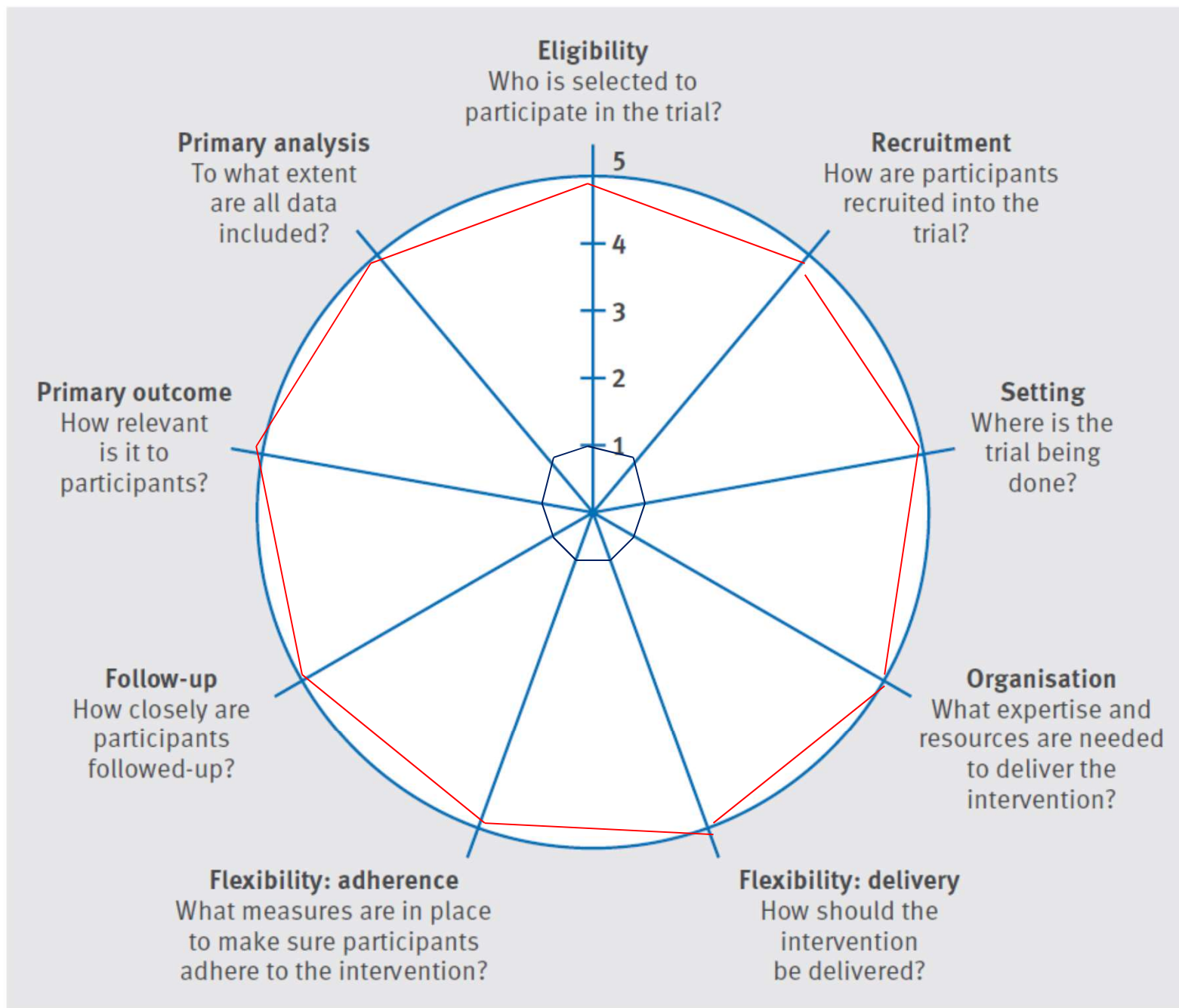
¹Health Services Research Unit,
University of Aberdeen,

²North York General Hospital,
Toronto, ON M2K 1E1, Canada

³Division of Population Health
Sciences, University of Dundee,

PRECIS is a tool to help trialists make design decisions consistent with the intended purpose of their trial. This paper gives guidance on how to use an

Key to this reward is that the trial can indeed support end user decisions in the ways intended by the trial design team. That this is not always, or even mostly, the case was highlighted nearly 50 years ago, by Schwartz and Lellouch in their paper on pragmatic and explana-



The PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel.

Pragmatic	Explanatory
Representative participants	Highly selected participants
Recruited in usual care, many centres	Recruited in another way, few centres
Setting where results apply	Different setting
Intervention “slotted” into usual care	Intervention requires additional resources
Flexibility in delivery	Very standardised delivery
Flexibility in adherence	Highly controlled adherence
Follow-up exactly as would be in usual care	More extensive follow up
Primary outcome relevant to participants	Primary outcome not relevant to participants
Primary analysis intention to treat	Primary analysis per protocol

When?

Translational research

makes findings from basic science useful for enhancing human health and well-being – “bench to bedside”

At the end of translational pathway – often drug development

Implementation research

is the scientific study of methods to promote the uptake of research findings

Development of intervention and trial design using UK Medical Research Council Framework for Complex Interventions (2000, 2006)

No other possibility

WAIT – Montelukast for pre-school wheeze

Population



Intervention



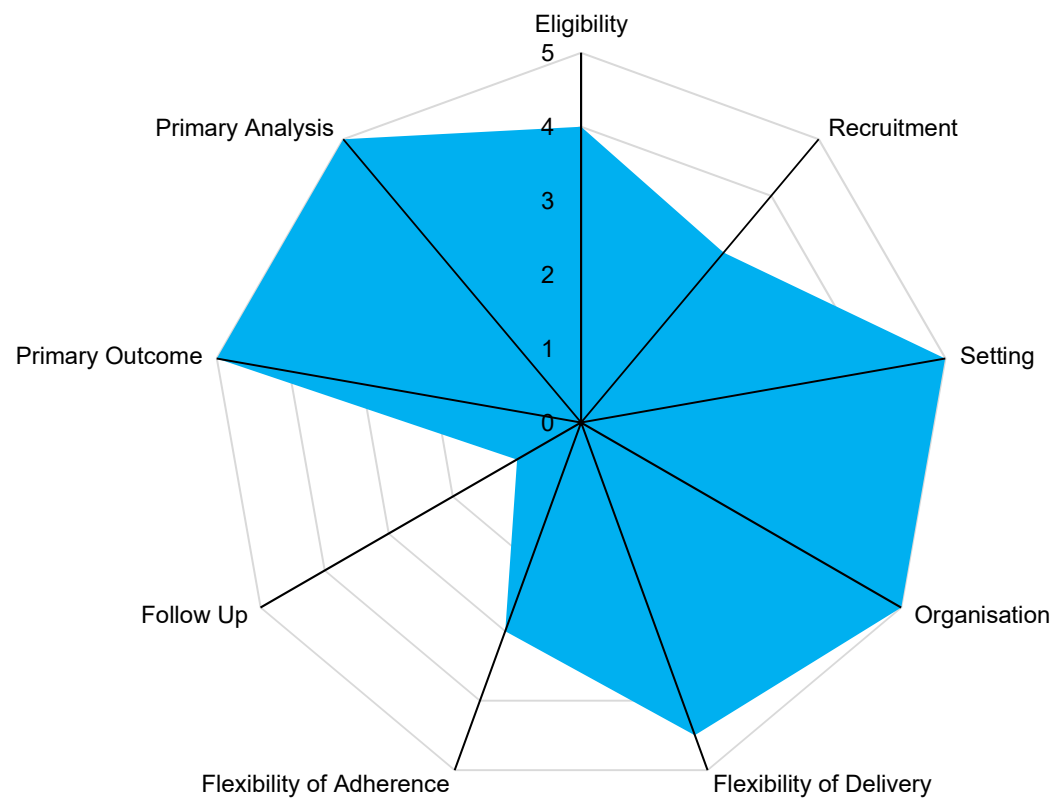
Outcome

Unscheduled
medical
attendances
for wheezing

Control

Placebo

WAIT



STOP – Smoking cessation through pharmacies

Population



Intervention

Training and support for pharmacists

Outcome (customers)



Control

No training and support

NESS - treating negative symptoms of schizophrenia

Intervention



Population

People with
schizophrenia

Outcome

Control (placebo)

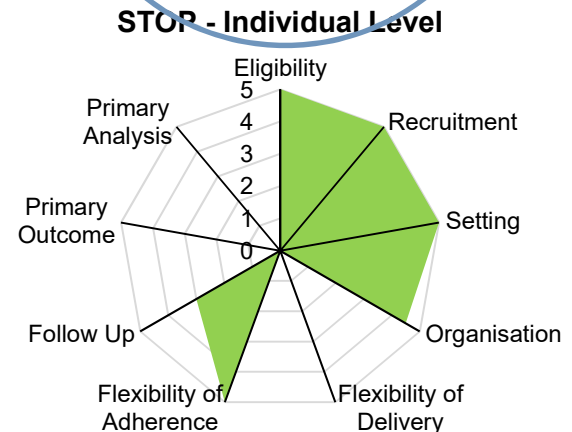
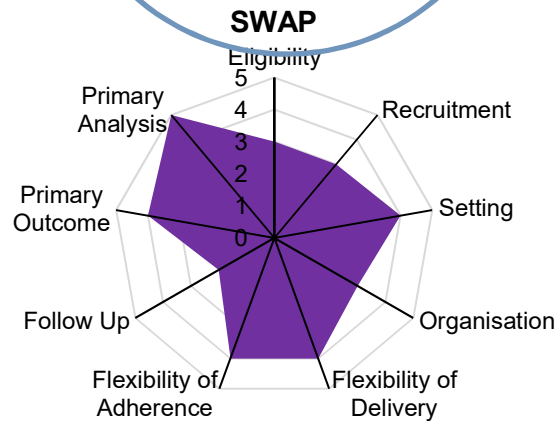
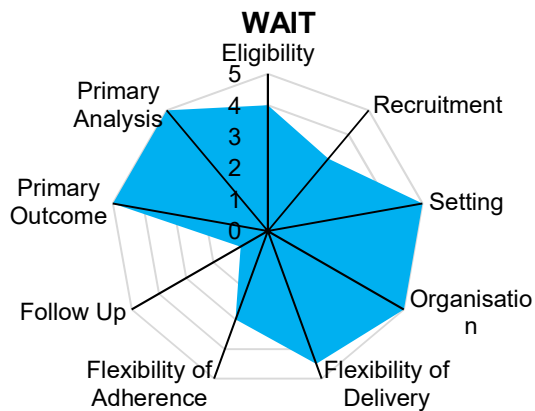
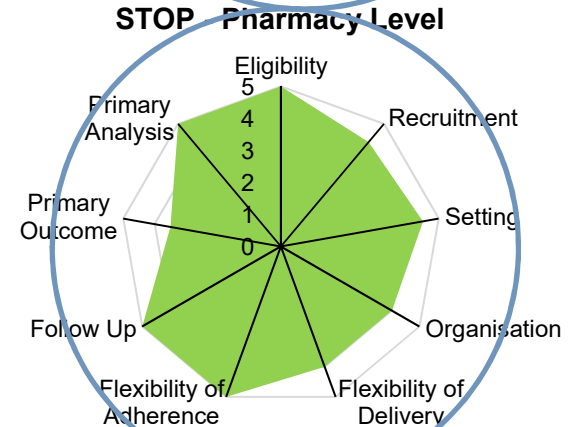
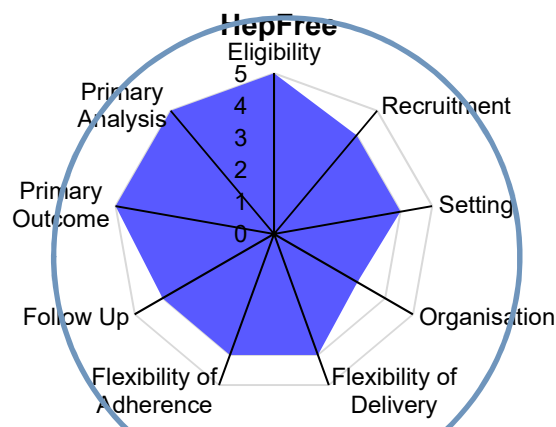
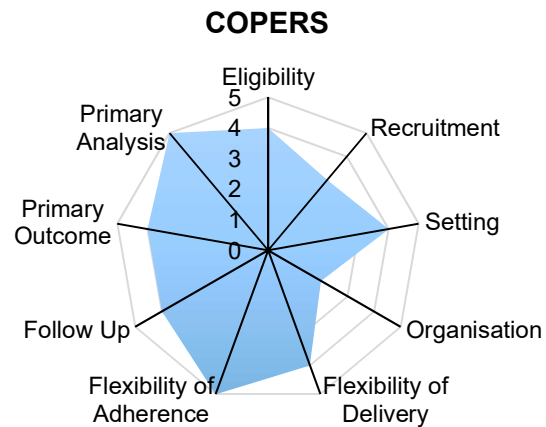
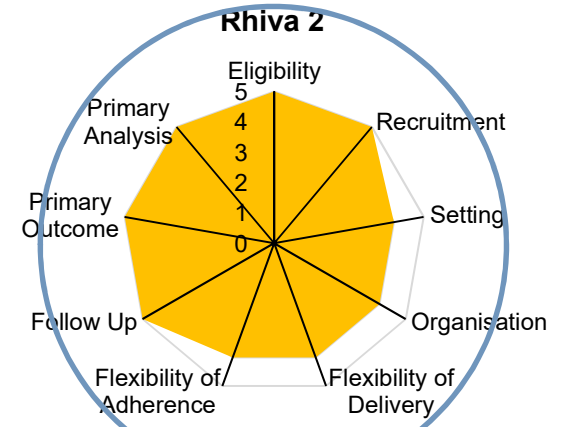
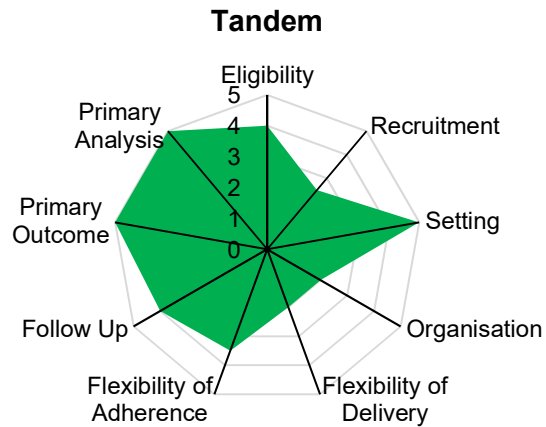


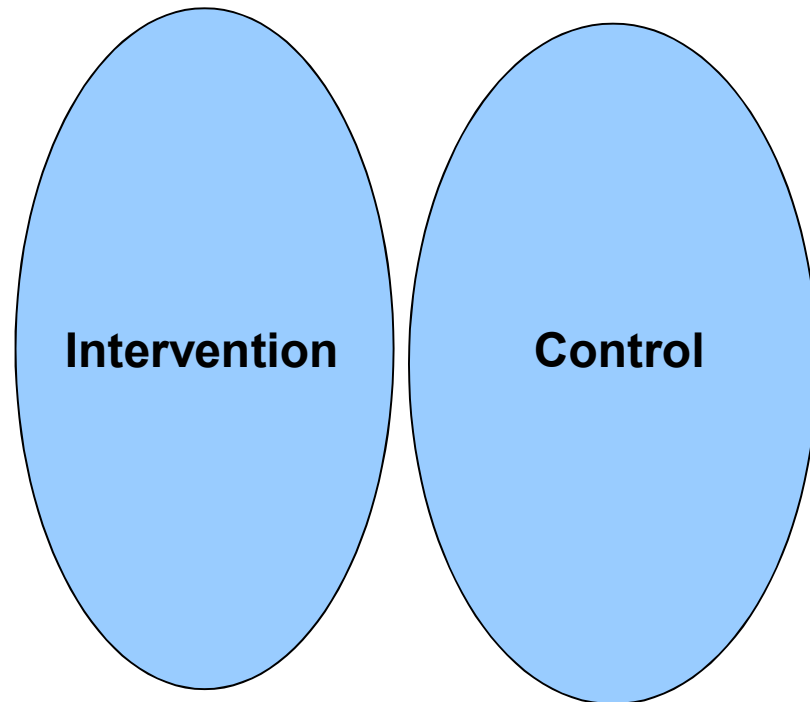
P A N S S
Positive and Negative Syndrome Scale



MHS

How pragmatic are **PCTU** trials?





Cluster randomised trial

**Cluster
randomized
trials**

Why cluster randomise?

- Contamination at individual level
- Contamination at professional level
- Intervention acts at cluster level
- Practical, financial, enhanced compliance

Results of randomising by cluster

- **Need larger sample size** (Rutterford IJE 2015)
- **Need to take account of clustering in analysis** (Books: Eldridge & Kerry 2012, Campbell & Walters 2014)
- **Intervention development complex** (MRC framework 2000, 2006; papers on pilot & feasibility studies)
- **Ethical issues (eg consent) different** (Ottawa statement, 2012)
- **Specific bias** (Farrin 2005 Clin. Trials, Eldridge 2008, 2009 BMJ, Cochrane ROB-2
<https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool>)

Identification/recruitment bias in cluster randomised trials

Aim: To improve back pain

Clusters: UK General Practices

Intervention: offer of exercise classes, physiotherapy etc.

Control group:

66 recruited

Intervention group:

165 recruited, suffering from milder back pain

Explanation: participation in the trial very attractive in intervention arm



Cluster 'consent'

Cluster randomisation

Participant consent to randomisation?

Participant consent to data collection, participation

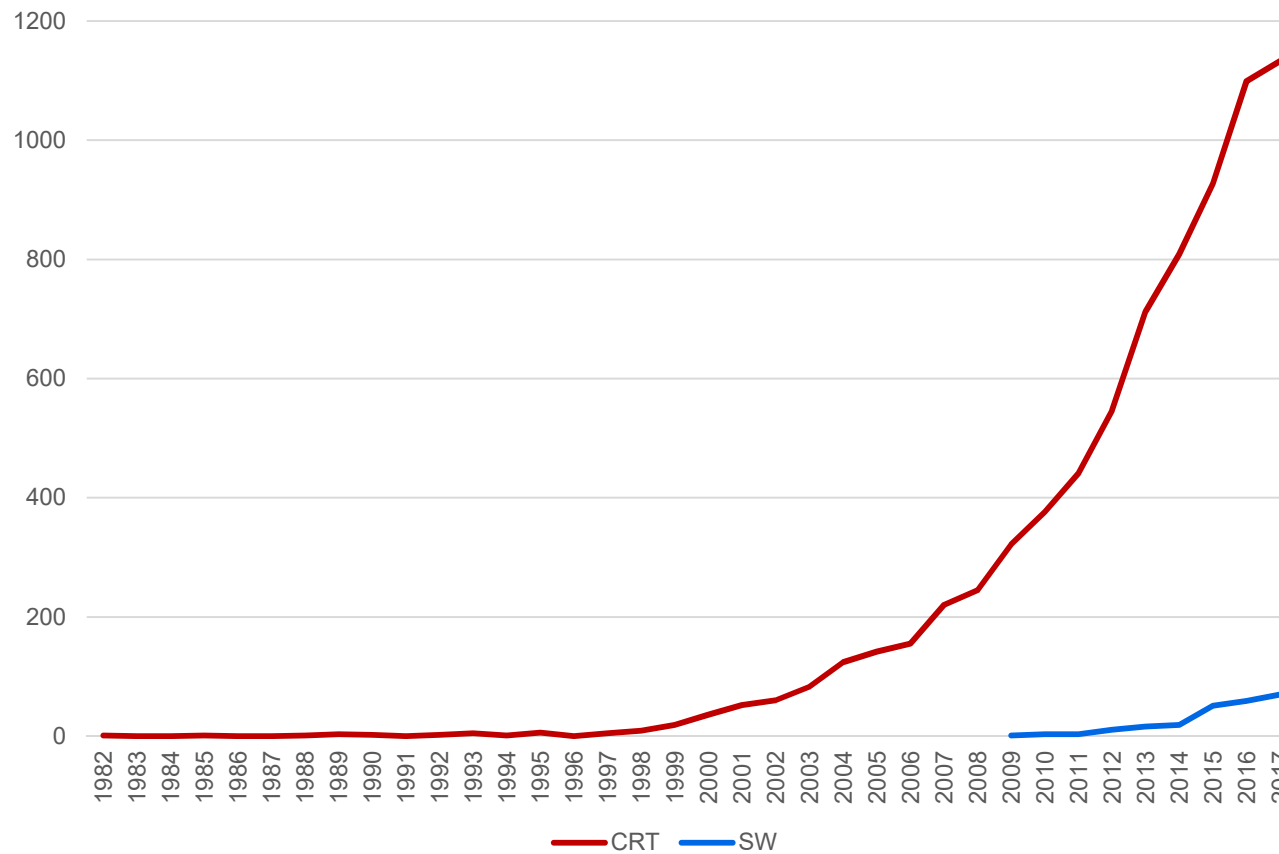
Study at BEH M pilot
Bias

Current issues

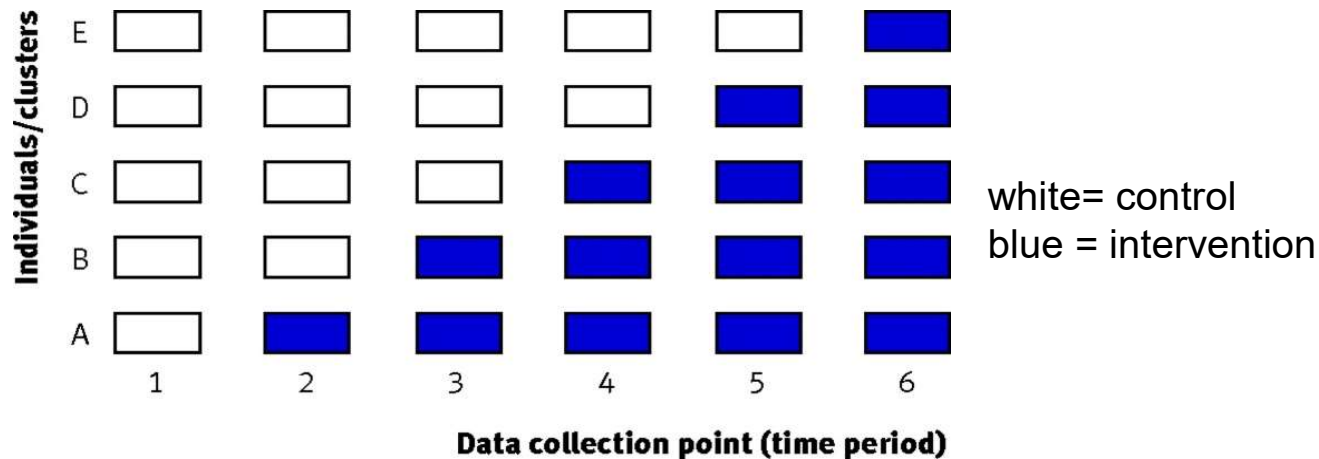
- Designing internal studies to assess feasibility
- Covariate constrained randomization
- Analysis with an assessment of outcome at baseline
- Causal treatment effects: instrumental variable methods
- New Cochrane risk of bias tool
- Treatment non-compliance
- Treatment contamination
- Small sample corrections: power and type I error rate
- Do cluster randomised and individually randomised trials estimate the same intervention effect?
- Adaptive designs

Cluster randomised trials and stepped wedge designs

Publications with "cluster randomi" and "stepped-wedge" in the
title 1982-2017



Stepped wedge designs



Increasingly popular design

Start with all units in control arm

End with all units in intervention arm

Units gradually included in intervention arm over time in random order

Four stated advantages of stepped wedge designs (Kotz 2012)

1. All participants receive the intervention
2. Sequential implementation of the intervention is advantageous
3. The stepped wedge design allows an intervention to be improved during the study

(all of these design features can operate in a classic cluster randomised trial)

4. Stepped wedge designs require fewer clusters compared with classic cluster RCTs *(but you may need more measurements)*

In addition the tight design means it is not possible to add clusters if cluster size is not as large as predicted

Issues

Zhan 2013 - colorectal cancer follow-up study

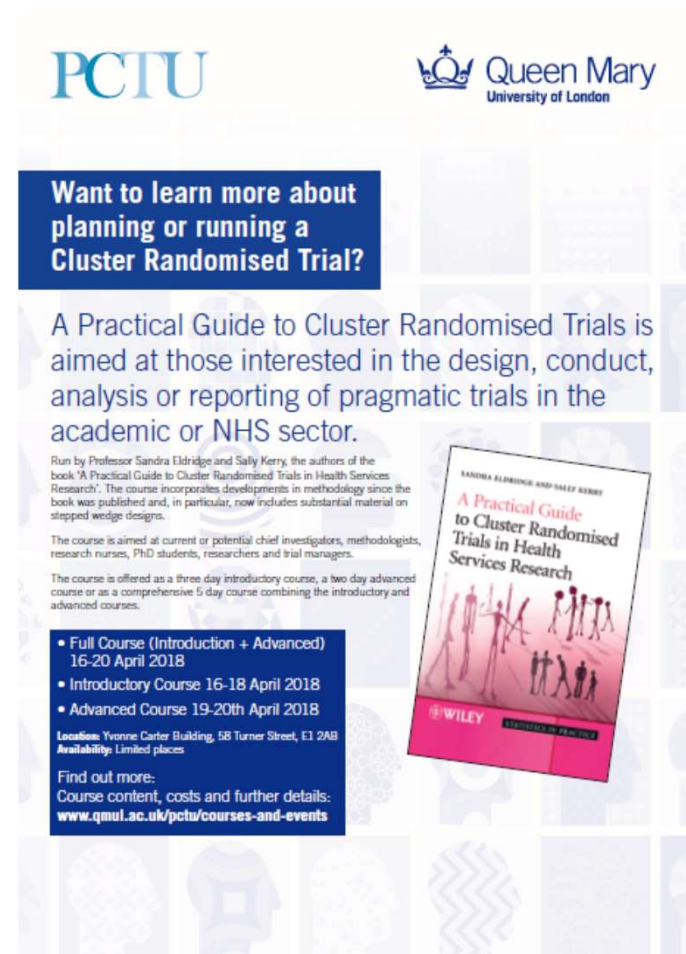
“A main advantage of the stepped wedge design was that the intervention rolls out to all participants, motivating patients and doctors, and a large number of patients who were included in this study. The stepped wedge design increased the complexity of the data analysis, and there were concerns regarding the informed consent procedure. The repeated measurements may bring burden to patients in terms of quality of life, satisfaction, and costs.”

Design and analysis

- Straightforward stepped wedge may not be most efficient (Girling & Hemming 2016)
- Some period-groups contribute much more information than others
- Different (and sometimes complex) biases not well understood yet
- Upcoming CONSORT extension will help!

Summary

- Pragmatic trials can arise in different ways
- PRECIS-2 useful
- Cluster randomised trials complex
- Stepped-wedge trials at same stage as cluster randomised trials were at the turn of the century



The flyer is for a course titled 'A Practical Guide to Cluster Randomised Trials'. It features the PCTU logo and the Queen Mary University of London crest. A blue box at the top asks 'Want to learn more about planning or running a Cluster Randomised Trial?'. The main text describes the book 'A Practical Guide to Cluster Randomised Trials in Health Services Research' by Sandra Eldridge and Sally Kerry, and the course itself. A list of course options is provided, along with the location and availability. A small image of the book cover is shown on the right.

PCTU **Queen Mary**
University of London

Want to learn more about planning or running a Cluster Randomised Trial?

A Practical Guide to Cluster Randomised Trials is aimed at those interested in the design, conduct, analysis or reporting of pragmatic trials in the academic or NHS sector.

Run by Professor Sandra Eldridge and Sally Kerry, the authors of the book 'A Practical Guide to Cluster Randomised Trials in Health Services Research'. The course incorporates developments in methodology since the book was published and, in particular, now includes substantial material on stepped wedge designs.

The course is aimed at current or potential chief investigators, methodologists, research nurses, PhD students, researchers and trial managers.

The course is offered as a three day introductory course, a two day advanced course or as a comprehensive 5 day course combining the introductory and advanced courses.

- Full Course (Introduction + Advanced) 16-20 April 2018
- Introductory Course 16-18 April 2018
- Advanced Course 19-20th April 2018

Location: Yvonne Carter Building, 58 Turner Street, E1 2AB
Availability: Limited places

Find out more:
Course content, costs and further details:
www.qmul.ac.uk/pctu/courses-and-events

A Practical Guide to Cluster Randomised Trials in Health Services Research
SANDRA ELDRIDGE AND SALLY KERRY
WILEY
EVIDENCE IN REALITY

April 16th to 20th 2018

<http://www.qmul.ac.uk/pctu/courses-and-events/>