Methodological issues in the design and analysis of cluster randomised trials

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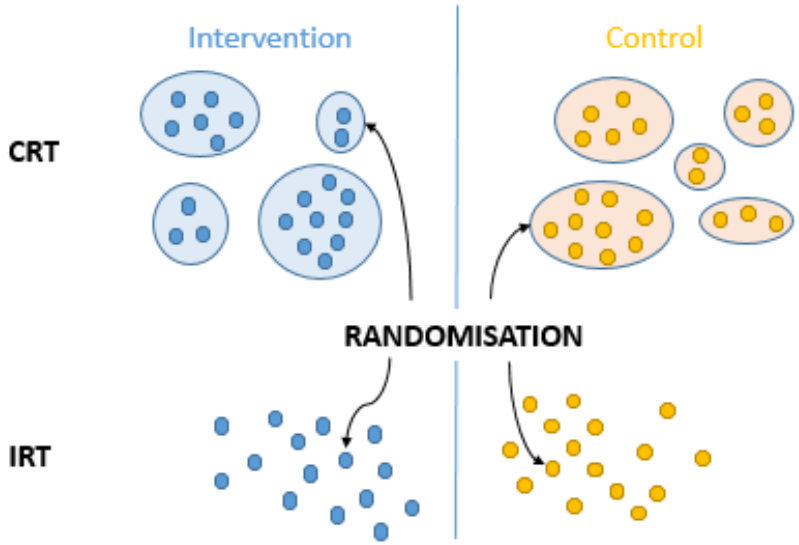
Cluster randomised trials

In randomised trials, **different randomisation units** can be used (participants or clusters of participants)

CRT: Cluster Randomised Trial
IRT: Individually Randomised Trial

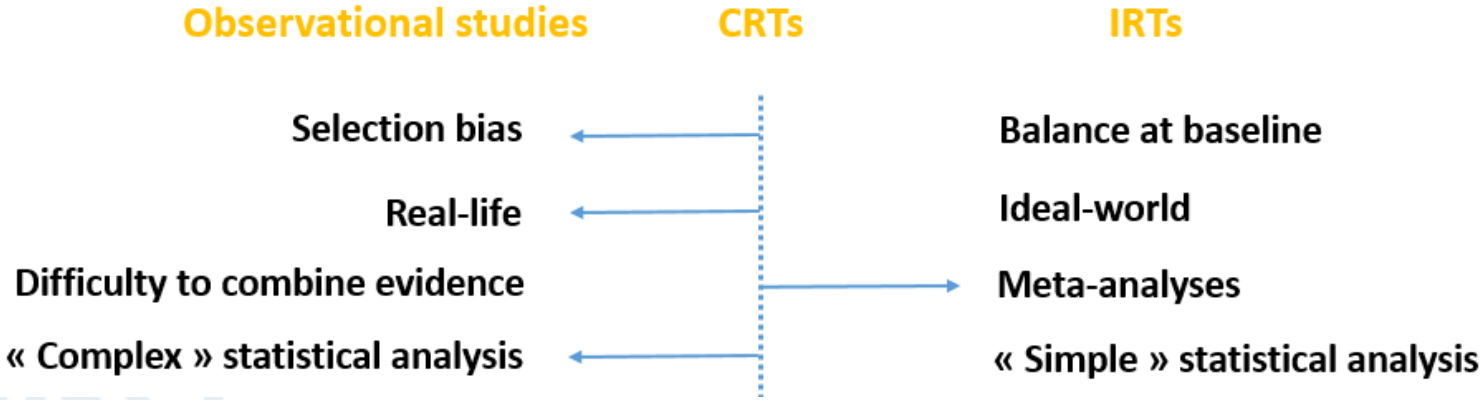


The similarity of the observations within the same cluster is quantified by the **intraclass correlation coefficient** (ICC)

Background
CRTs
Challenges
Bias
Pragmatism
Statistical analysis
Small-sample
The ICC
Discussion

Trials or observational studies?

CRTs share characteristics with IRTs and observational studies:



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Biases in CRTs:

How to detect them in CRTs

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Biases in CRTs

In CRTs, bias can arise from the design, according to:

- the chronology
- recruitment procedure
- blinding

Development of a graphical tool[1]: **Timeline cluster**

[1] Caille *et al.*. Timeline cluster: a graphical tool to identify risk of bias in cluster randomised trials.BMJ. 2016;354:i4291

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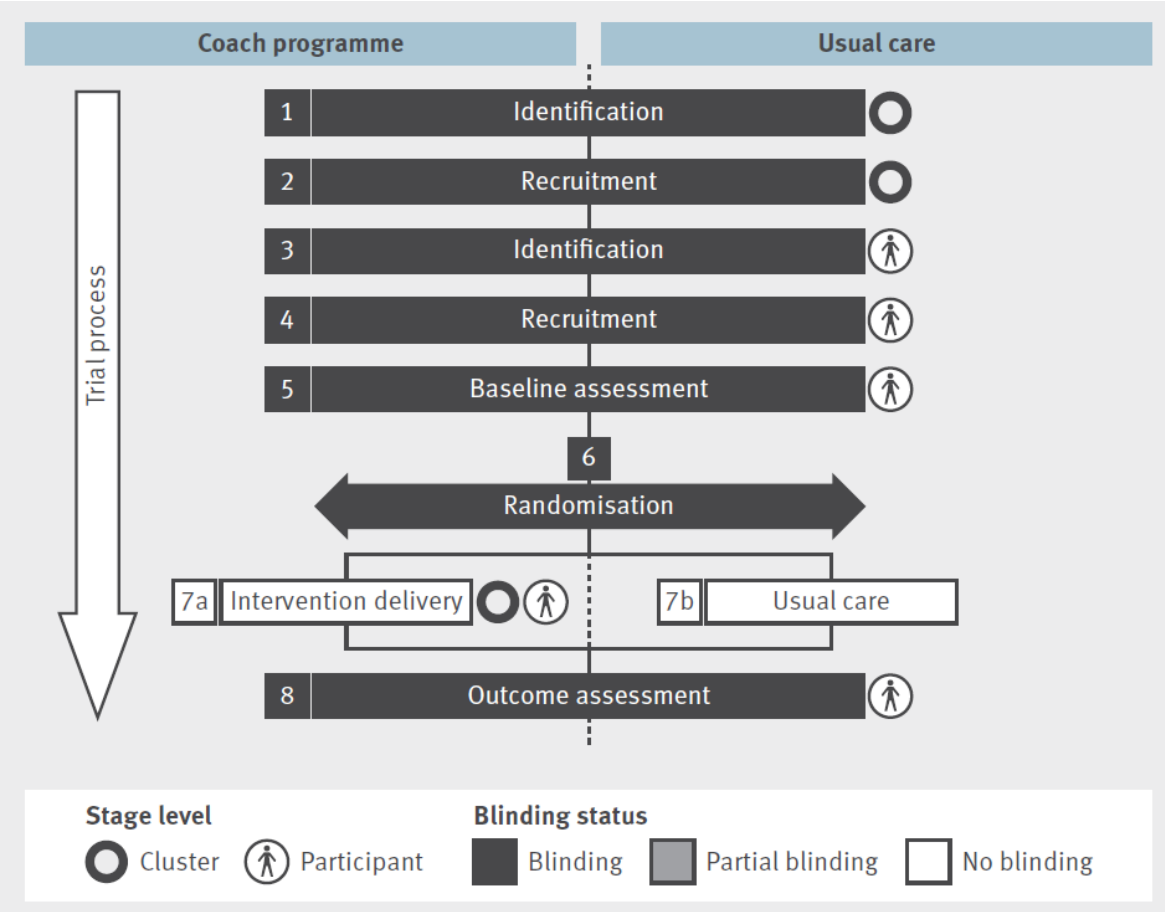
Timeline cluster



Recruitment bias ✓
Performance bias ✗
Detection bias ✓

Clusters: GP practices in Australia
Intervention: Nurse training on coaching on glycaemic control of type 2 diabetes
Outcome: Glycated haemoglobin

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In practice...

Timeline cluster is a **qualitative tool** to identify the risk of bias

Can be adapted for more complicated designs such as cluster cross-over designs

This graph should be reported in protocols and publications

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Pragmatism in CRTs:

Do CRT and IRT estimate the same effects? Can we meta-analyse them together?

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MEpiCluster

CRTs are thought to be **more pragmatic** than IRTs

How does it impact **intervention effect estimates**?

$\Longrightarrow$ Disagreements in the literature

Meta-epidemiological study to compare intervention effect estimates in CRTs and IRTs:

- Inclusion of Cochrane systematic reviews
- 76 meta-analyses with a binary outcome:
  917 trials: 734 IRTs and 183 CRTs
- 45 meta-analyses with a continuous outcome:
  541 trials: 410 IRTs and 131 CRTs

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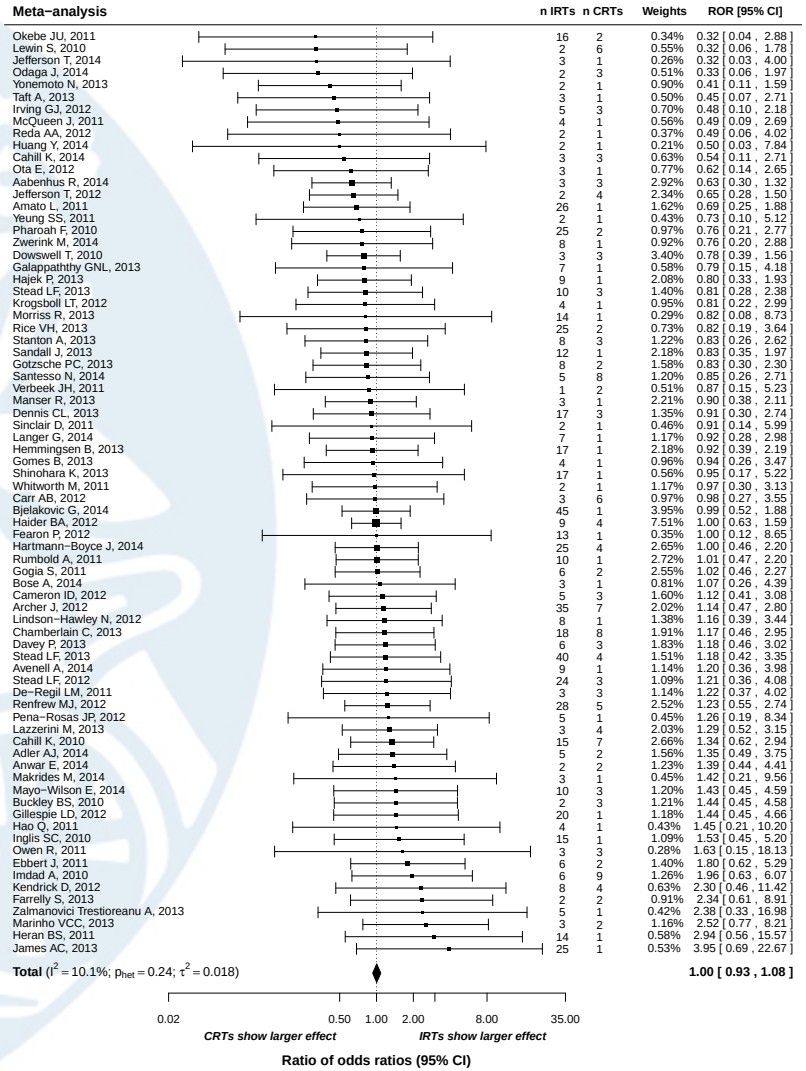
Results



For **binary outcomes**:
ROR=1.00 [0.93;1.08]

Similar result in **subgroups**:

- ✓ objective v. subjective
- ✓ pharmacological v. non pharmacological
- ✓ active v. inactive control

For **continuous outcomes**:
DSMD=0.13 [0.06;0.19]

- ✗ high heterogeneity
- ✗ no difference when adjusting on sample size

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Implications

From this study, **no substantial differences** between intervention effect estimates from IRTs and CRTs:

- They can be **meta-analysed together** IF clustering accounted for properly
- They estimate the "same" effect

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Statistical analysis:

The intraclass correlation

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Small sample size

3 main approaches to analyse CRTs: cluster-level analyses, mixed-models or GEEs

When only few clusters are randomised: **inflated type I error rate** for mixed-models and GEEs

Small-sample corrections available in standard software packages but:

- Not often implemented in practice[1]
- Negative impact on **power**

[1] Kahan *et al.* Increased risk of type I errors in cluster randomised trials with small or medium numbers of clusters: a review, reanalysis, and simulation study. Trials. 2016 Sep 6;17(1):438.

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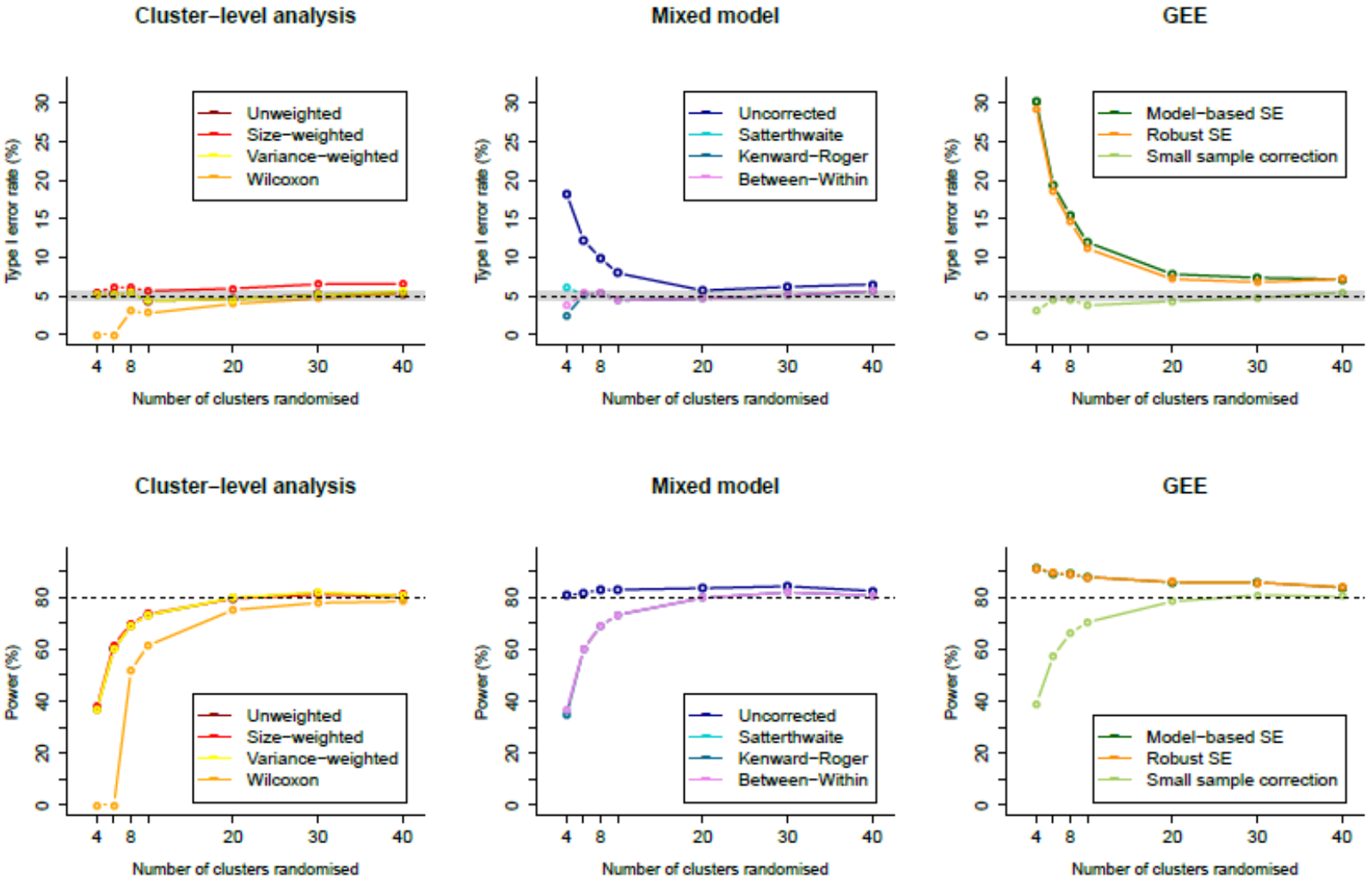

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The ICC: an outcome?

The variation of the ICC could be useful in providing information about the **heterogeneity of the intervention effect**

$\Longrightarrow$ Should this difference be **reported** along with the outcome?

For binary outcomes, the ICC depends on the prevalence

$\Longrightarrow$ **Difficult to interpret** if there is a positive intervention effect

Ongoing work on the **rescaling of binary ICCs** to make them independent of the prevalence

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Discussion

Challenges in the design and analysis of CRTs not encountered in IRTs:

- Risk of selection bias
- Correlation in the data
- ...

However, the conclusions from CRTs are **similar** to those from IRTs whilst avoiding limitations in the implementation of IRTs

A lot of unresolved questions...

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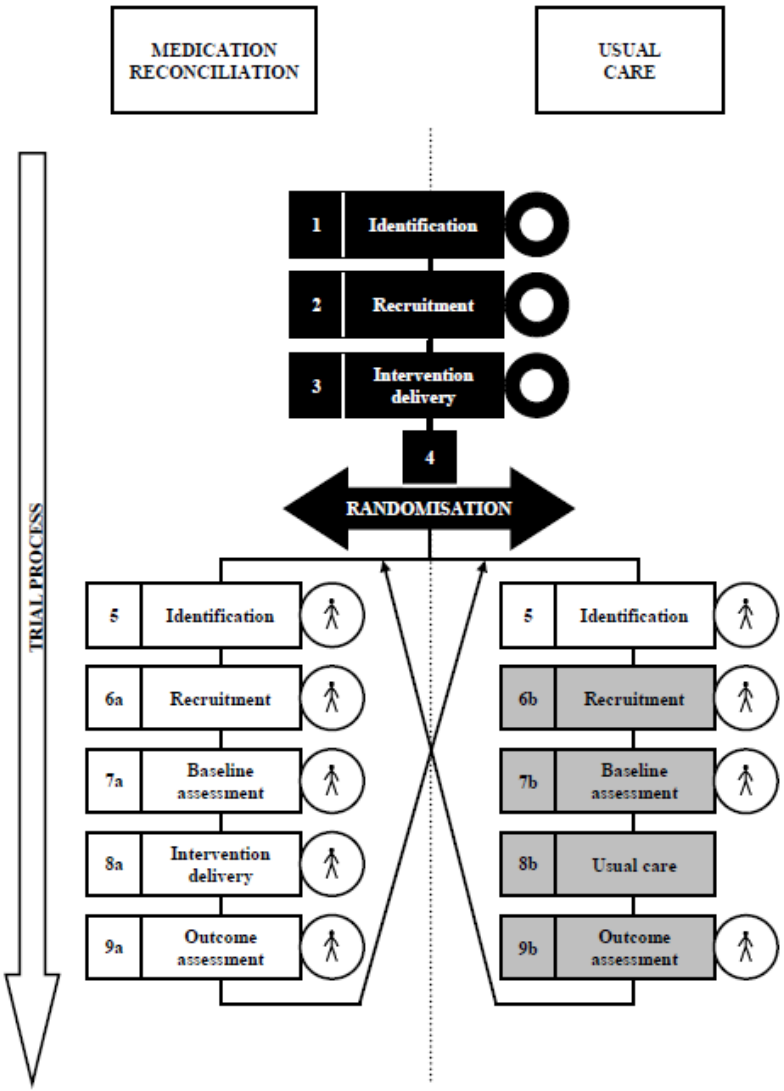
Timeline cluster (2)



Cluster cross-over trial
Clusters: hospital wards
Intervention: medication reconciliation
Outcome: drug-related problem

Recruitment bias ✗
Performance bias ✗
Detection bias ✗

Rescaling the ICC

Ongoing work on the **rescaling of binary ICCs** to make them independent of the prevalence

Arm	Prevalence (%)	Binary ICC	Continuous ICC
Malathion	85.0	0.44	0.74
Ivermectine	95.2	0.61	0.95