



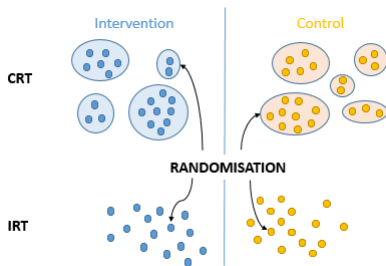
Methodological issues in the design and analysis of cluster randomised trials

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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

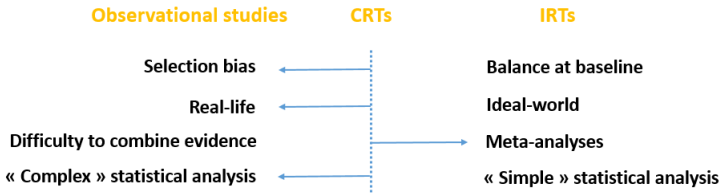
Small-sample

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

- ▶ the chronology
- ▶ recruitment procedure
- ▶ blinding

Development of a graphical tool¹: **Timeline cluster**

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

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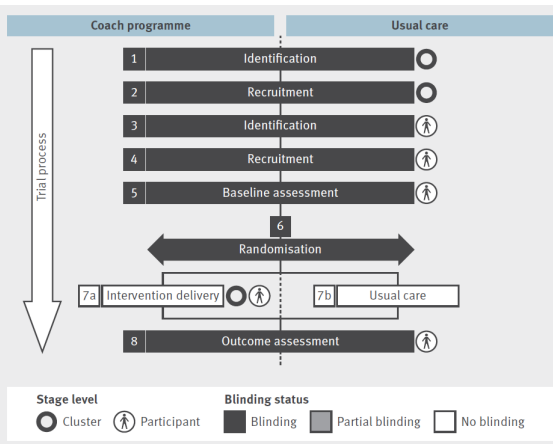
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Timeline cluster



Recruitment bias ✓
Performance bias ✗
Detection bias ✓

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Clusters: GP practices in Australia

Intervention: Nurse training on coaching on glycaemic control of type 2 diabetes

Outcome: Glycated haemoglobin



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

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

⇒ 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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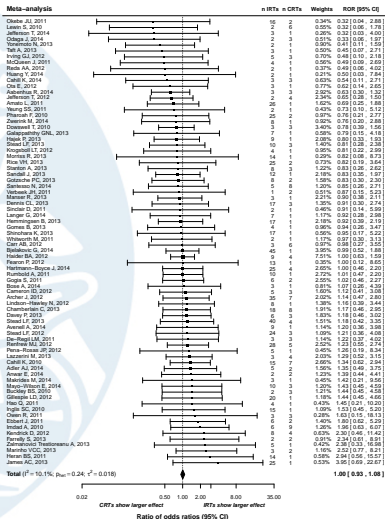
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Results



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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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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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 practice¹
- ▶ Negative impact on **power**

¹Kahan *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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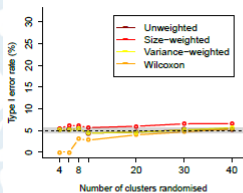
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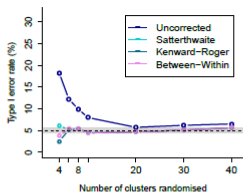
Small sample size



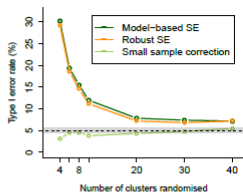
Cluster-level analysis



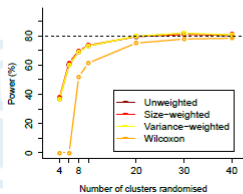
Mixed model



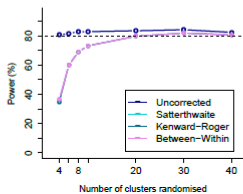
GEE



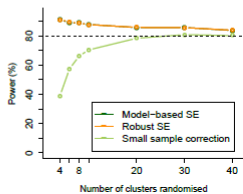
Cluster-level analysis



Mixed model



GEE



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

⇒ Should this difference be **reported** along with the outcome?

For binary outcomes, the ICC depends on the prevalence

⇒ **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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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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Acknowledgements



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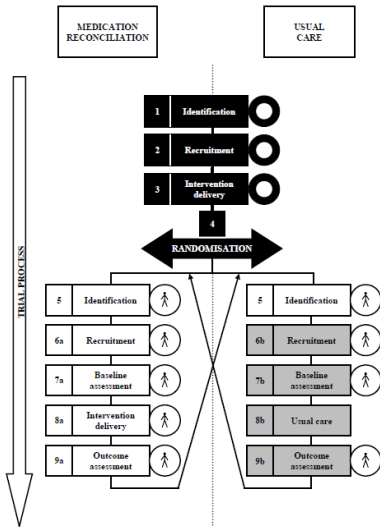
Baptiste Leurent
Katy Morgan



Allan Donner



Timeline cluster (2)



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

Recruitment bias ✗
Performance bias ✗
Detection bias ✗



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

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