New Cochrane risk of bias tool for cluster randomised tools: extension to stepped wedge designs

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Outline

The new Cochrane risk of bias tool (ROB-2)
Methods and scope
Results and application to stepped wedge designs
Cochrane ROB-2

Need for revision of original ROB tool identified
Predominantly for systematic reviewers
Funded by MRC Network of Hubs for Trials Methodology Research
Evidence that about 10% of reviews include cluster randomised trials
What about stepped wedge designs?
Also useful for thinking about bias more generally
ROB-2-cRCT: methods and overall results

Sub-group of group updating main ROB-2
Mostly teleconferences and emails over a long period of time!
Adaptation of main tool
Used expertise and personal collections of trials
Piloting amongst group and externally
Continuous referral back to main group

Of 5 domains in updated main tool:
Adaptations to three domains
Added one new domain

Scope:
All types of clusters in which individuals are the cluster members
All types of clustered randomised design including stepped wedge
Domains for ROB-2-cRCT

Domain 1a: Bias arising from the randomisation process

Domain 1b: Timing of identification and recruitment of individual participants in relation to timing of cluster randomisation

Domain 2: Bias due to deviations from the intended intervention (blinding)

Domain 3: Bias due to missing outcome data

Domain 4: Bias in measurement of the outcome

Domain 5: Bias in selection of the reported result
In each domain

Series of signalling questions to which answers can be yes, probably yes, no, probably no, unknown

Answers are used in an algorithm to identify likelihood of bias
Preliminaries: outcomes and participants

Tool assumes risk of bias being assessed for a single outcome
For cluster randomised trials “participants” = target individuals on whom it has been decided to collect the outcome of interest

<table>
<thead>
<tr>
<th>IRIS trial</th>
<th>Open access urology trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clusters: general practices</td>
<td>Clusters: general practices</td>
</tr>
<tr>
<td>Intervention: to increase identification and referral for victims of domestic violence</td>
<td>Intervention: guideline-based open access urological investigation service</td>
</tr>
<tr>
<td>No individual participant recruitment</td>
<td>Outcome: <em>general practitioners’</em> compliance with referral guidelines</td>
</tr>
<tr>
<td>Data collection: routine records <em>of all women in practice aged 16 plus</em></td>
<td>Outcome: waiting time for <em>patients’</em> referral</td>
</tr>
</tbody>
</table>
Domain 1a: Bias arising from the randomisation process (*allocation concealment*)

Key fact: clusters can be randomised sequentially, in batches, or all at once

<table>
<thead>
<tr>
<th>IRIS trial</th>
<th>Diabetes manual trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clusters <em>randomised sequentially</em></td>
<td>Clusters <em>randomised in batches</em></td>
</tr>
<tr>
<td>Cluster identified, details emailed to allocator, allocator emailed back allocation status</td>
<td>Stratification factors largely aggregated participant baseline data</td>
</tr>
</tbody>
</table>

Comments:

👍 Less easy to subvert randomisation in cluster randomised trials

👎 More difficult to judge whether baseline imbalances are indicative of problems with randomisation process
Domain 1a in stepped wedge trials

Clusters usually randomised all at once
Allocation could be concealed from clusters until cross-over

Comments:

- Subversion of randomisation not an issue

- Will anything be different if allocation revealed at the start of the trial or at the point of cross-over?
Domain 1b: Timing of identification and recruitment of individual participants in relation to timing of cluster randomisation (new domain)

Key fact: The timing of cluster randomisation, participant identification and participant recruitment (if relevant) can be a potential source of bias in cluster randomised trials in a way that is not possible in individually randomised trials
<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4 (identical to 6)</th>
<th>Scenario 5</th>
<th>Scenario 6 (identical to 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster randomization</td>
<td>Cluster randomization</td>
<td>Identification of potential individual participants</td>
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<td>Identification of potential individual participants</td>
<td>Identification of individual participants</td>
<td>Cluster randomization</td>
<td>Cluster randomization</td>
<td>Recruitment of individual participants</td>
<td>Participants not directly recruited</td>
</tr>
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<td>Participants not directly recruited</td>
<td>Cluster randomization</td>
<td>Cluster randomization</td>
</tr>
<tr>
<td><strong>Potential for identification/recruitment bias although this could be avoided through trial design</strong></td>
<td><strong>No potential for identification/recruitment bias because randomization happens after</strong> UK BEAM pilot (Farrin et al 2005)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Two further examples in which identification/recruitment bias possible

**Scenario 2: Feeding strategies for critically ill patients in intensive care**
- **Clusters:** Intensive care unit (ICU) wards
- **Intervention:** Guidelines developed by ICU staff
- **Outcome:** Hospital discharge mortality
- **Participants:** Not directly recruited but identified by ICU staff (though no evidence of bias)

**Scenario 3: Hip protectors for preventing hip fractures**
- **Clusters:** Elderly care units within community based health centres
- **Participants:** Identified prior to randomisation but approached after randomisation
- **Recruited:** 31% in intervention and 9% in control group

[www.qmul.ac.uk/pctu](http://www.qmul.ac.uk/pctu)
Domain 1b in stepped wedge trials

**Design**
- Closed cohort
- Open cohort
- Cross-sectional

**If any participants identified and/or recruited after randomisation, bias possible**

**Bias occurs if differential recruitment between intervention and control periods**
HELP: Quality Improvement intervention to prevent delirium in Dutch hospital

“The Medical Ethical Review Board unexpectedly required written pre-treatment informed consent from every individual patient, whereas we intended to provide a safe quality improvement intervention, requiring only post-treatment consent for using existing clinical data and completion of a short questionnaire...... The required written informed consent most likely decreased the number of patients enrolled into our study and might have also introduced a selection bias.” (Trials 2016)
Domain 1b in stepped wedge trials

Possible routes to avoiding/reducing bias if participants identified/recruited after randomisation:
- Standardise identification
- Recruit outside the cluster
- Use masked recruiters
- Do not recruit

BMJ 2009

Cross-sectional, surgery: “Patients will be informed about the study at the outpatient clinic. The patient will be included upon admission after informed consent has been obtained.”

RESEARCH METHODS & REPORTING

Bias in identifying and recruiting participants in cluster randomised trials: what can be done?

Sandra Eldridge, Sally Kerry, David J Torgerson

Blinded recruitment of participants presents particular challenges for cluster trials, but careful design can minimize the risk of selection bias.

What needs reporting and how in order for readers to judge the likelihood of bias?
Domain 2: Bias due to deviations from the intended intervention (*blinding*)

Key facts:
Interventions often multifaceted, aimed at various participants and participants and others cannot be blinded *to the intervention*

Know about trial *and* which intervention they are getting, that is when bias occurs

In an individually randomised trial with blinded placebo participants know they are in a trial but *not* which intervention they are getting....
Domain 2: signalling questions

Do participants (for the outcome of interest) know they are in a trial? (sometimes no)

If they know they are in a trial, are they aware of their assigned intervention? (usually yes)

Are there other people involved in the intervention who know the allocation of participants? (often yes)

If participants or others are aware of assigned intervention did this affect the way the intervention was delivered beyond what one would expect in usual practice?

Those who might have the opportunity to introduce deviations to the intervention might have little inclination to do so

The more complex the intervention the more difficult to identify potential deviations

Likely that information reported is limited
Domain 2 Algorithm

2.1a Participant aware they are in a trial? or 2.1b Participant aware of intervention?

2.2 Personnel aware of intervention?

(2.1a or 2.1b) and 2.2 N/PN

(2.1a and 2.1b) or 2.2 Y/PY/Ni

2.3 Any deviations from intended intervention?

Y/PY

N/PN

Ni

2.4 Deviations unbalanced and affect outcome?

Y/PY

N/PN

Ni

2.5a and 2.5b Clusters or participants analysed in wrong group?

2.6 Could affect outcome?

2.5a and 2.5b Clusters or participants analysed in wrong group?

2.6 Could affect outcome?

Low risk

Some concerns

High risk

Some concerns

High risk
Domain 2 in stepped wedge trials

Individual participants or others
Aware in trial and aware of intervention period

*Differential effect on care delivery before and after cross-over, beyond what one would expect “in usual practice”?*
Domain 3: Bias due to missing outcome data

Key fact:
Missingness can occur at both cluster and individual level

Comment:
Need to be careful about interpretation of bias caused by missing clusters as will depend on the reasons for missing
- Missing because dropped out very early on
- Missing because did not recruit any participants
- Missing because data not available on any participants
Domain 3 in stepped wedge trials

Additional reasons for differential drop out?
More acute in cohort designs?
When clusters cross-over?
In clusters that cross-over late on?
Domains 4 & 5: Bias in measurement of outcome and in selection of reported outcome

Broadly similar issues in individually and cluster randomised trials

Key issues for domain 4:
  - Objective measures
  - Blinding of assessor
Additional source of bias in stepped wedge trials mentioned in guidance:

This includes stepped-wedge trials in which randomization is by cluster, although there is a source of bias in these trials if they are analysed without adjustment for secular trends which is not directly covered in the tool (1).
Questions for stepped wedge trial experts!

When should allocation be revealed?
How should identification and recruitment be reported so that the likelihood of bias can be judged?
Could there be a differential effect on care delivery before and after cross-over beyond usual practice?
What reasons could there be for differential drop-out given the length of time of the trial?
What other sources of bias might there be?