Cochrane Revised Risk of Bias Tool (RoB 2)

Additional Considerations for Cluster-Randomized Trials

Sandra Eldridge
Revised Cochrane risk of bias tool for randomized trials (RoB 2)
Additional considerations for cluster-randomized trials (RoB 2 CRT)

Sandra Eldridge, Marion K Campbell, Michael J Campbell, Amy K Drahota, Bruno Giraudreau, Barnaby C Reeves, Nandi Siegfried, Julian PT Higgins
10 November 2020

www.qmul.ac.uk/pctu
Six domains

1a Bias arising from the randomization process
1b Bias arising from the identification or recruitment of participants into clusters
2 Bias due to deviations from intended intervention
3 Bias due to missing outcome data
4 Bias in measurement of the outcome
5 Bias in selection of the reported result
Domain 1a: Bias arising from the randomization process

1.1 Allocation sequence random?

1.2 Allocation sequence concealed?

1.3 Baseline imbalances suggest a problem?

Low risk

Some concerns

High risk
Baseline imbalances in cluster randomised trials

Randomisation at cluster level
- Review baseline imbalances primarily at cluster level

Small numbers of clusters
- Chance imbalances more common
- Harder to predict how clusters will respond & less chance of subversion
- Problems with randomisation less likely

Domain 1b
- Another possible reason for imbalance
### OPERA trial – Underwood et al Lancet 2013

Randomising residential care homes, whole-home activity intervention to reduce depression

<table>
<thead>
<tr>
<th></th>
<th>All care homes *</th>
<th>Study care homes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Intervention</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>323 (100%)</td>
<td>78 (24%)</td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nursing</td>
<td>81 (25%)</td>
<td>18 (23%)</td>
</tr>
<tr>
<td>Residential</td>
<td>242 (75%)</td>
<td>60 (77%)</td>
</tr>
<tr>
<td><strong>Ownership</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>262 (81%)</td>
<td>61 (78%)</td>
</tr>
<tr>
<td>Voluntary or charity</td>
<td>36 (11%)</td>
<td>16 (21%)</td>
</tr>
<tr>
<td>Local authority</td>
<td>25 (8%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td><strong>Size</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;32 beds</td>
<td>158 (49%)</td>
<td>43 (27%)</td>
</tr>
<tr>
<td>≥32 beds</td>
<td>165 (51%)</td>
<td>35 (73%)</td>
</tr>
<tr>
<td><strong>Mean number of beds (SD)</strong></td>
<td>34.89 (19.62)</td>
<td>31.41 (11.49)</td>
</tr>
<tr>
<td><strong>Median cohort participants per home (IQR)</strong></td>
<td></td>
<td>11 (8-15)</td>
</tr>
</tbody>
</table>
Domain 1b: Bias arising from the identification or recruitment of participants into clusters

1b.1 All participants identified/recruited before randomization?

1b.2 Selection of participants affected by knowledge of intervention?

1b.3 Baseline imbalances that suggest differential identification/recruitment?

Low risk

Some concerns

High risk

NEW
Selecting individual participants

Participants = target individuals on whom it has been decided to collect the outcome of interest

Participants may not be recruited
Participants may be clinicians as well as patients

If patients are recruited after randomisation someone involved may know about allocation

Bias may ensue
Recruitment and randomisation

**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

Bias study - WKBEAM pilot.
<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3 (identical to 6)</th>
<th>Scenario 4 (identical to 6)</th>
<th>Scenario 5 (identical to 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster randomization</td>
<td>Cluster randomization</td>
<td>Identification of potential individual participants</td>
<td>Identification of individual participants</td>
<td>Identification of potential individual participants</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>Recruitment of individual participants</td>
<td>Participants not directly recruited</td>
<td>Recruitment of individual participants</td>
<td>Participants not directly recruited</td>
<td>Cluster randomization</td>
</tr>
<tr>
<td>Potential for identification/recruitment bias although this could be avoided through trial design</td>
<td></td>
<td></td>
<td></td>
<td>No potential for identification/recruitment bias because randomization happens after</td>
</tr>
</tbody>
</table>

UK BEAM pilot (Farrin et al 2005)
Two further examples in which identification/recruitment bias possible

**Scenario 2: Feeding strategies for critically ill patients in intensive care**

<table>
<thead>
<tr>
<th>Clusters: Intensive care unit (ICU) wards</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention: Guidelines developed by ICU staff</td>
</tr>
<tr>
<td>Outcome: Hospital discharge mortality</td>
</tr>
<tr>
<td>Participants not directly recruited but identified by ICU staff (though no evidence of bias)</td>
</tr>
</tbody>
</table>

**Scenario 3: Hip protectors for preventing hip fractures**

<table>
<thead>
<tr>
<th>Clusters: Elderly care units within community based health centres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants identified prior to randomisation but approached after randomisation</td>
</tr>
<tr>
<td>Recruited: 31% in intervention and 9% in control group</td>
</tr>
</tbody>
</table>
Domain 1b: Bias arising from the identification or recruitment of participants into clusters

1b.1 All participants identified/recruited before randomization? [Y/PY]

1b.2 Selection of participants affected by knowledge of intervention? [N/PN/NI]

1b.3 Baseline imbalances that suggest differential identification/recruitment? [N/PN/NI]

Low risk

High risk

Some concerns

NEW
Once care homes had agreed to participate, we invited residents to give written, informed consent, or if they lacked capacity to consent, for their next of kin to give written, informed agreement for us to collect data directly from participants, from care-home staff, and from care-home and National Health Service (NHS) records.

We recruited additional participants for 9 months after randomisation for an end of study cross-sectional analysis, using the same criteria as described previously.
Bias assessed separately for different outcomes - OPERA trial as an example

**Outcome 1: GDS-15 score at 12 months for those depressed at baseline**
Includes only individuals recruited before randomisation

**Outcome 2: Being depressed at end of study**
Includes individuals recruited before and after randomisation
Domain 1b: Bias arising from the identification or recruitment of participants into clusters

Outcome 1: Clearly low risk

1b.1 All participants identified/recruited before randomization?
   - Y/PY

1b.2 Selection of participants affected by knowledge of intervention?
   - N/PN/NI

1b.3 Baseline imbalances that suggest differential identification/recruitment?
   - Y/PY

Low risk

Some concerns

High risk
The prevalence of depression in all residents at the end of the study is an important analysis to ensure the findings apply to all residents rather than only relatively healthy survivors. In this analysis we recruited more participants in the intervention homes than in the control homes after randomisation. Results were, however, unchanged by excluding the post randomisation participants.
Domain 1b: Bias arising from the identification or recruitment of participants into clusters

Outcome 2: Some concerns

But, only a small % of participants recruited post randomisation?
Domain 2: Bias due to deviations from intended intervention (assignment)

Part 1: Questions 2.1 to 2.5

2.1a Participants aware they are in a trial?
- Y/PY/NI

2.1b Participants aware of intervention?
- Both N/PN
- Either Y/PY/NI

2.2 Personnel aware of intervention?
- N/PN

2.3 Deviations that arose from the experimental context?
- N/PN
- Y/PY

2.4 Deviations balanced between groups?
- N/PN
- N/NI

2.5 Deviations affect outcome?
- Y/PY/NI

Low risk

Part 2: Questions 2.6 & 2.7

2.6 Appropriate analysis to estimate the effect of assignment?
- Y/PY
- Low risk

2.7 Substantial impact of the failure to analyse participants in randomized groups?
- N/PN/NI
- Some concerns

High risk

Criteria for the domain

- ‘Low risk’ of bias in Part 1 AND ‘Low risk’ of bias in Part 2 → Low risk
- ‘Some concerns’ in either Part 1 or in Part 2, AND Not ‘High risk’ in either Part → Some concerns
- High risk in either Part 1 or in Part 2 → High risk
IRIS trial, Feder et al, Lancet 2011

Randomising UK general practices, intervention to increase identification of and referral for domestic violence

Because the intervention was targeted at clinicians and administrators and no consent was required for outcome data extraction from medical records, as agreed by the research ethics committee, patients were not aware they were part of a research study.
Domain 2: Bias due to deviations from intended intervention (assignment)

Part 1: Questions 2.1 to 2.5

2.1a Participants aware they are in a trial?
- Y/PY/NI

2.1b Participants aware of intervention?
- Both N/PN

2.2 Personnel aware of intervention?
- Y/PY/NI

2.3 Deviations that arose from the experimental context?
- N/PN

2.4 Deviations balanced between groups?
- N/PN/NI

2.5 Deviations affect outcome?
- Y/PY/NI

Part 2: Questions 2.6 & 2.7

2.6 Appropriate analysis to estimate the effect of assignment?
- Y/PY
  - Low risk

2.7 Substantial impact of the failure to analyse participants in randomized groups?
- N/PN/NI
  - Some concerns

Criteria for the domain:

- ‘Low risk’ of bias in Part 1 AND ‘Low risk’ of bias in Part 2 → Low risk
- ‘Some concerns’ in either Part 1 or in Part 2, AND Not ‘High risk’ in either Part → Some concerns
- High risk in either Part 1 or in Part 2 → High risk
Researchers collecting follow-up data from individual participants, and the participants themselves, were inevitably aware of home randomisation because of the physiotherapists’ activities within the home.

OPERA trial –
Underwood et al Lancell 2013

Randomising residential care homes, whole-home activity intervention to reduce depression
Domain 2: Bias due to deviations from intended intervention (assignment)

Part 1: Questions 2.1 to 2.5
- 2.1a Participants aware they are in a trial? (Y/P/N/NI)
- 2.1b Participants aware of intervention? (Y/P/N/NI)
- 2.2 Personnel aware of intervention? (N/P/N)
- 2.3 Deviations that arose from the experimental context? (Y/P/N)
- 2.4 Deviations balanced between groups? (Y/P/N/NI)
- 2.5 Deviations affect outcome? (Y/P/N/NI)

Part 2: Questions 2.6 & 2.7
- 2.6 Appropriate analysis to estimate the effect of assignment? (Y/P)
- 2.7 Substantial impact of the failure to analyze participants in randomized groups? (Y/P/N/NI)

Criteria for the domain:
- 'Low risk' of bias in Part 1 AND 'Low risk' of bias in Part 2 → Low risk
- 'Some concerns' in either Part 1 or in Part 2, AND Not 'High risk' in either Part → Some concerns
- High risk in either Part 1 or in Part 2 → High risk
Domain 2: Bias due to deviations from intended intervention (assignment)

Part 1: Questions 2.1 to 2.5

- **2.1a Participants aware they are in a trial?**
  - Y/P/Y/NI
  - N/P/N

- **2.1b Participants aware of intervention?**
  - Either Y/P/Y/NI
  - Both N/P/N

- **2.2 Personnel aware of intervention?**
  - N/P/N

- **2.3 Deviations that arose from the experimental context?**
  - N/P/N

- **2.4 Deviations balanced between groups?**
  - Y/P/Y
  - N/P/N

- **2.5 Deviations affect outcome?**
  - Y/P/Y/NI
  - Low risk

Part 2: Questions 2.6 & 2.7

- **2.6 Appropriate analysis to estimate the effect of assignment?**
  - Y/P/Y
  - Low risk

- **2.7 Substantial impact of the failure to analyze participants in randomized groups?**
  - N/P/Y/NI
  - Some concerns

Criteria for the domain:

- 'Low risk' of bias in Part 1 AND 'Low risk' of bias in Part 2
  - Low risk

- 'Some concerns' in either Part 1 or in Part 2, AND Not 'High risk' in either Part
  - Some concerns

- High risk in either Part 1 or in Part 2
  - High risk
Intention to treat analyses in cluster randomised trials

**Cohort design:** Recruit participants at baseline and follow-up

Similar to individually randomised trial, analyse in clusters that they were recruited to

**Cross-sectional design:** Collect data on cross-section at end of the trial

Can assume that analysing in clusters from which data arose is sufficient in most cases

**Repeated cross-sectional design:** Collect data on different cross-sections at start and end

Can make similar assumptions as for cross-sectional designs
OPERA was a mixture of cohort and cross-sectional designs

For cohort analyses we included residents in the home from which they were recruited. For cross-sectional analyses we included residents in the home in which they were resident at the end of the study.

OPERA trial – Underwood et al Lancet 2013
Randomising nursing homes, whole-home activity intervention to reduce depression
Domain 3: Bias due to missing outcome data

3.1a Outcome data for all clusters?
3.1b Outcome data for all participants?

3.2 Evidence that result is not biased?

3.3 Missingness could depend on true value?

3.4 Likely that missingness depended on true value?

Decision:
- Both Y/PY: Low risk
- Either N/PN/NI: Low risk
- Y/PY: Some concerns
- N/PN: Some concerns
- Y/PY/NI: High risk
- N/PN: High risk
Principles for assessing missingness need to be applied at both individual and cluster level.

- Missingness related to outcome?
- Missingness differential between arms?
Domain 4: Bias in measurement of the outcome

4.1 Method of measuring the outcome inappropriate?

4.2 Measurement or ascertainment of outcome different between groups?

4.3a Outcome assessors aware of trial taking place?

4.3b Outcome assessors aware of intervention received?

4.4 Could assessment have been influenced by knowledge of intervention?

4.5 Likely that assessment was influenced by knowledge of intervention?

Low risk

Some concerns

High risk
Domain 5: Bias in selection of the reported result

NO CHANGES

5.1 Trial analysed in accordance with a pre-specified plan?
- Y/Py → Low risk
- N/PN/Ni → Some concerns
- Both N/PN → High risk

Result selected from...
- ...multiple outcome measurements? 5.2
- ...multiple analyses of the data? 5.3
# Additional Considerations for Cluster-Randomized Trials

<table>
<thead>
<tr>
<th>Bias</th>
<th>Description</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Bias arising from the randomization process</td>
<td>Unchanged, assessment needs to account for small numbers of clusters and domain 1b</td>
</tr>
<tr>
<td>1b</td>
<td>Bias arising from the identification or recruitment of participants into clusters</td>
<td>Consider whether participants aware in trial, may be difficult to identify deviations</td>
</tr>
<tr>
<td>2</td>
<td>Bias due to deviations from intended intervention</td>
<td>Consider whether participants aware in trial, may be difficult to identify deviations</td>
</tr>
<tr>
<td>3</td>
<td>Bias due to missing outcome data</td>
<td>Consider at cluster as well as individual level</td>
</tr>
<tr>
<td>4</td>
<td>Bias in measurement of the outcome</td>
<td>Consider whether outcome assessors aware in trial</td>
</tr>
<tr>
<td>5</td>
<td>Bias in selection of the reported result</td>
<td>No changes</td>
</tr>
</tbody>
</table>