Cluster Randomised Trials in Injury Research: A How-To Guide

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Workshop Objectives

- Decide who should consent to participation
- Understand how to address refusals and withdrawals
- Address risks for bias unique to CRTs
- Identify an appropriate intracluster correlation coefficient and apply it to sample size estimation
- Recognize need to take clustering into account in analyses
- Justify use of CRT (if time allows)

Workshop Format

- Introduction
- Brief Presentations
  - Consent
  - Design / Bias
  - Sample size and Analysis
  - Justification (if time allows)
- Interactive ‘How-To’ Sessions – choice of two
  - Determining Who/When to Consent
  - Addressing Potential Biases
  - Sample Size Calculation
- Close

Definition of Cluster Randomised Trial (CRT)

- Random allocation of existing groups of individuals to study arms
  - E.g., Family, Classroom, Church, Clinic, Neighborhood

Questions?

Consent Issues in Cluster Randomised Trials

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Consent

• ‘Cluster-cluster trials’
  – the intervention is aimed at clusters
    • E.g., Mass media campaigns or laws
• ‘Individual-cluster trials’
  – the intervention is delivered to individuals within clusters
    • E.g., safety counselling for clinic patients

Cluster-Cluster Trials

• If the cluster participates, cluster members MUST participate
  – Only option for individual refusal is to leave the cluster
• Therefore, MUST obtain appropriate ‘cluster consent’ that represents cluster members’ interests

Cluster-Cluster Trials

• Who gives cluster consent?
  – Usually ‘guardian’ with administrative responsibility for cluster (e.g., headteacher, city council)
  – May establish independent “cluster representation mechanism” (CRM) (individual or body) to safeguard interests of cluster members

Cluster-Cluster Trials

• Role of the Guardian/CRM
  – Weigh risks/benefits for cluster
    • May directly assess member interests (e.g., survey)
  – Provide consent if benefits outweigh risks
  – Remain informed about study progress
  – Withdraw cluster if risk/benefit ratio changes

Cluster-Cluster Trials

• All individual cluster members should (in general) be provided with information about the trial
  – Can give their opinion to the guardian/CRM
  – If possible, opt out of participation or data use

Individual-Cluster Trials

• MUST obtain appropriate ‘cluster consent’
• After cluster enrolment, individual members can accept or decline participation
  – E.g., in intervention clinics, individual patients can accept or decline safety counselling
• Therefore, individual consent should also be obtained from all participants
  • Ideally, from all participants prior to cluster randomization
Withdrawals in CRTs

- If cluster guardian wishes to withdraw cluster
  - Guardian may withdraw cluster at any time
  - All members of that cluster are also withdrawn; cannot continue even if they wish to
    - Could transfer to a participating cluster if they have been informed about trial
  - In general, cluster members should be informed of withdrawal from study

Withdrawals from CRTs

- If individual cluster member wishes to withdraw
  - Cluster-cluster trials
    - Cannot withdraw (except transfer out of cluster)
    - Should inform guardian of desire to withdraw and reasons (e.g., adverse effects)
    - Guardian may then choose to withdraw entire cluster
  - Individual-cluster trials
    - Individual may withdraw anytime
    - Researchers should inform guardian of withdrawals and the reasons (typically in aggregate)
    - Guardian may then choose to withdraw entire cluster

Interactive ‘How-To’ Session: Determining Who & When to Consent

- Consenting cluster ‘guardian’
- Assessing cluster members’ interests
- Consenting individual cluster members
- Addressing refusals and withdrawals

Questions?

Plan

- What is bias?
- Types of bias particularly relevant to C-RCTs
- How can bias be avoided or minimised?
- Practical: what we will cover

Study Design Issues

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**What is bias?**

- "A bias is a systematic error, or deviation from the truth, in results or inferences" [www.cochrane-handbook.org](http://www.cochrane-handbook.org)
- Systematic distortion of the estimated intervention effect away from the "truth", caused by inadequacies in the design, conduct, or analysis of a trial [www.consort-statement.org](http://www.consort-statement.org)
- Systematic = consistently "wrong" in one or other direction

**Specific bias issues in C-RCTs**

<table>
<thead>
<tr>
<th>Type</th>
<th>How it may occur</th>
<th>Strategies to prevent bias</th>
</tr>
</thead>
</table>
| Selection bias     | - Simple randomisation of small numbers of clusters - "chance" imbalance between groups - Cluster members know allocation at time of recruitment - post randomisation recruitment bias   | - Stratified randomisation, minimisation or matched pair design  
- Randomise after all clusters & members recruited  
- Blunt & consent blind to allocation  
- Use design without cluster member consent                                                                                           |
| Attrition bias     | - Higher dropout in control clusters/members - not receiving "favoured" intervention or receiving less attention - Higher dropout in intervention clusters/members - study demands  | - Waiting list controls  
- Alternative "active" control condition  
- Clarity of expectations at cluster/member level  
- No withdrawn option e.g. geographic units in consenting community  
- Intention to treat analysis                                                                                                           |
| Dilution bias      | - Intervention not received by members due to refusal post randomisation - Migration out of clusters - Control group may receive intervention                                                               | - Include refusal/consent before randomisation  
- Rigorous methods of follow-up  
- Geographic separation of groups  
- Inflated sample size  
- Measure compliance at cluster & member level & account for in analysis                                                                 |

**Post-randomisation recruitment bias**

<table>
<thead>
<tr>
<th>Plan to use walker</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>25%</td>
<td>37%</td>
</tr>
<tr>
<td>No</td>
<td>49%</td>
<td>37%</td>
</tr>
<tr>
<td>Unsure</td>
<td>26%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Intervention group less likely to plan to use a baby-walker—likely to lead to overestimation of treatment effect

Proventing child safety in primary care: a cluster randomised controlled trial to reduce baby walker use.
Kendrick D et al, BMJ 2005; 331:582-588

**Specific bias issues in C-RCTs**

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| Detection bias     | Differences between groups in how outcomes are determined                                             | - Outcome assessors & participants not blind to allocation so outcomes ascertained differentially between groups  
- Blind clusters +/- members to allocation  
- Blind outcome assessors to allocation  
- Use objectively measured outcomes  
- Use routinely collected data                                                                                       |
| Dilution bias      | Differences between groups in receipt of allocated intervention                                         | - Exclude refusal/consent before randomisation  
- Rigorous methods of follow-up  
- Geographic separation of groups  
- Inflated sample size  
- Measure compliance at cluster & member level & account for in analysis                                                                 |

**Attrition bias**

Cycle helmet promotion trial: 28 eligible schools randomised

14 brief intervention schools

- 100% completed baseline assessment
- 77% completed follow up assessment
- 98% completed follow up assessment

Possibly less interested children/teachers did not respond in brief intervention group — may lead to underestimation of treatment effect.

Kendrick D, Young S. Cycle helmet ownership and use: a cluster randomised controlled trial in primary school children in deprived areas. Arch Dis Child 2004; 89:130-134

**Possible detection bias**

<table>
<thead>
<tr>
<th>Self reported outcomes</th>
<th>Intervention group</th>
<th>Control group</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involved in child injury prevention</td>
<td>58%</td>
<td>25%</td>
<td>1.5 (1.2, 2.1)</td>
</tr>
<tr>
<td>Believes could take action to help prevent child injuries in their ward</td>
<td>73%</td>
<td>53%</td>
<td>1.4 (1.2, 1.6)</td>
</tr>
</tbody>
</table>

**Objective outcomes**

- Percentage of kilometres of road traffic calming per ward (median, IQR)
  - 14.9 (1.8 to 13.9)  
  - 14.6 (1.1 to 8.6)  
  - 0.1 (0.1 to 0.2)

Likely to lead to overestimation of treatment effect

Lyns M, Kendrick D, Taver N et al. The impact on active travel (Cycle-RT): reduce pedestrian deaths in deprived communities. [unpublished data]
Dilution bias

Home safety equipment trial

1100 families in intervention group
1019 families in control group

Interventions: Advice, home safety check, low cost safety equipment & first aid training.
N = 6 possible interventions/contacts

Number of interventions received:

0       = 243  (22%)
1 – 2   = 594  (54%)
3 – 4   = 241  (23%)
5 – 6   = 22    (2%)

Likely to lead to underestimation of treatment effect


Interactive ‘How-To’ Session: Identifying bias and how to avoid it

• Review extracts from published injury prevention C-RCTs
• Identify types of possible bias
• Determine how to avoid or minimise such bias

Questions?

Cluster randomised controlled trials: sample size and analysis

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Outline

› Effects of clustering
› Sample size calculations
› Analysis of cluster randomised trials
› Practical – working out some sample sizes

Clustering effects

› In cluster randomised trials participants in the same cluster tend to be more alike than participants in different clusters.
Members of the same cluster tend to respond to interventions in ways more similar to others in the same cluster than to members of different clusters, because:

- People who choose cluster are more similar to each other (e.g., school, church)
- Common exposures (e.g., busy street)
- Interact with each other (e.g., share information)

Thus, participant outcomes are usually correlated within clusters. This means usual methods of sample size calculation and analysis are not valid!

The intraclass correlation coefficient (ICC) measures similarity of people in the same cluster.

- It is the proportion of the total variation in the outcome of interest that occurs between clusters.
- Usually has positive values, with a maximum of 1.
  - If ICC = 0 → no clustering effects
  - If ICC = 1 → all people in the same cluster have the same value of the outcome

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Sample size needs to account for clustering.

First calculate sample size as if study was individually randomised trial (N_{IRT})

Then modify to allow for clustering, using an appropriate ICC value to calculate sample size for a cluster randomised trial (N_{CRT})

N_{CRT} = N_{IRT} \times (1 + (\text{cluster size} - 1) \times \text{ICC})

Sample size calculation

Analysis also needs to account for clustering, otherwise significance levels are likely to be too low and confidence intervals too narrow.

Two main approaches –

- Cluster level analyses
- Individual level analyses which account for clustering
Cluster level analysis: Combine/aggregate data for each cluster and compare treatment groups, e.g., Kendrick et al (1999) calculated injury rate in each practice and compared treatment groups with a t-test.

Individual level analysis: Use multi-level modelling, or generalised estimating equations.

Cluster randomisation affects sample size calculations and analysis of a trial. Sample sizes can be much larger than for individually randomised trials. Analyses which fail to account for clustering can give misleading results. These trials should be reported carefully (see CONSORT guidelines on cluster trials).

Justification for Using CRTs
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Why is Justification Necessary?
• CRTs are more complex to:
  – Consent
  – Design
  – Analyze
• Therefore, use of CRT design must be justified

Scientific Justification
• Potential contamination between groups
  – Intervention and control subjects in same social unit may share information or resources
    • E.g., in classroom, control child learns conflict resolution skills from a child trained in these skills as part of a violence prevention intervention
  – Cluster-level intervention
    – Intervention delivered to and affects groups of individuals
      • E.g., Media campaigns, organizational changes, laws
Logistical Justification

• Efficiency and cost
  – Concentrate activities in fewer locations, train fewer people to deliver intervention, access subjects more easily. E.g.:
  • Canvassing homes to deliver intervention
  • Training teachers to deliver violence prevention curriculum to students

• Access to routinely collected data
  • Outcome data for entire social unit may be routinely collected; protects confidentiality
  • E.g., Nursing home will release monthly report on aggregate falls, but not individually identifiable falls data

Questions?