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?

The University of Nottingham

Study Design Issues

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Plan

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

What is bias?

- "A **bias** is a systematic error, or deviation from the truth, in results or inferences" *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*
- Systematic = consistently "wrong" in one or other direction

Specific bias issues in C-RCTs

Type	How it may occur	Strategies to prevent bias
Selection bias Differences between baseline characteristics of groups	-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 -Recruit & consent blind to allocation -Use design without cluster member consent
Attrition bias Differences between groups in withdrawals	-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 withdrawal option e.g. geographic units in consenting community Intention to treat analysis

Post-randomisation recruitment bias

Plans to use walker	Intervention group	Control group
Yes	25%	37%
No	49%	37%
Unsure	26%	26%

Intervention group less likely to plan to use a baby walker– likely to lead to ***overestimation*** of treatment effect

Promoting child safety in primary care: a cluster randomised controlled trial to reduce baby walker use. Kendrick D et al, BJGP 2005; 55:582-588

Attrition bias

Cycle helmet promotion trial: 28 eligible schools randomised

14 brief intervention schools → **100% completed baseline assessment** → **77% completed follow up assessment**

14 intensive intervention schools → **100% completed baseline 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, Royal S. Cycle helmet ownership and use; a cluster randomised controlled trial in primary school children in deprived areas. Arch Dis Child 2004; 89:330-335.

Specific bias issues in C-RCTs

Type	How it may occur	Strategies to prevent bias
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	-Intervention not received by members due to refusal post randomisation -Migration out of clusters -Control group may receive intervention	-Exclude refusers/consent before randomisation -Rigorous methods of follow up -Geographic separation of groups -Inflate sample size -Measure compliance at cluster & member level & account for in analysis

Possible detection bias

Self reported outcomes	Intervention group	Control group	Effect size (95% CI)
Involved in child injury prevention	38%	25%	1.5 (1.1, 2.1)
Believes could take action to help prevent child injuries in their ward	73%	53%	1.4 (1.2, 1.6)
Objective outcomes			
Percentage of kilometres of road traffic calmed per ward (median, IQR)	4.9 (1.8 to 13.9)	4.6 (1.1 to 8.6)	0.1 (-0.1 to 0.2)

Likely to lead to ***overestimation*** of treatment effect

Lyons, RA, Kendrick D, Towner E et al. The Advocacy in Action Study: Cluster-RCT to reduce pedestrian injuries 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%)

Number interventions received:
1019 (100%) received usual care

Likely to lead to ***underestimation*** of treatment effect

Kendrick, D. et al. Preventing injuries in children: cluster randomised controlled trial. BMJ 1999; 318:980-983.

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?

The University of Nottingham

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

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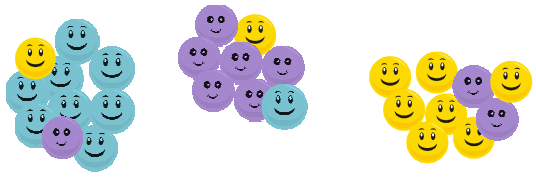
Clustering effects

- In cluster randomised trials participants in the same cluster tend to be more alike than participants in different clusters.



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Clustering effects

- Members of same cluster tend to respond to interventions in ways more similar to others in 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!

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Intraclass correlation coefficients

- 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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ICC values

- ICC values are generally below 0.2 in injury prevention studies
- See Handout for examples
- Studies of knowledge and behaviour in schools have reported higher ICCs
- ICC values are usually lower for larger clusters (e.g. geographical areas) and higher for smaller ones (e.g. families)

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Sample size calculation

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

DESIGN EFFECT

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Sample size – example

Intervention to reduce baby walker use

- **Individually randomised trial:**
  To detect 10% reduction in use, from 50%, with 80% power and 5% significance, **388** mothers are needed per study arm
- **Cluster randomised trial:**
  Clustered by general practice.
  Assume ICC = 0.017, average cluster size=23
- N_{CRT} = 388 x (1 + (23-1) x 0.017)
  = 388 x 1.37
  = 532

  i.e. now **532** mothers are needed per study arm
  So 532/23 = **23 practices** are needed **per study arm**.

(Kendrick et al. Br J Gen Pract 2005;55:582-8)

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Analysis

- 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

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Analysis

- 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.

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Conclusions

- 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).

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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

Justification

- Scientific justification
- Logistical justification

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?