Analysis of Cluster Randomized Trials

Fundamental Concepts

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Overview

- What are cluster randomized trials?
- Why do we do them?
- Implications for sample size and analysis
- Simple methods based on cluster summaries
- Adjusting for covariates
- Regression methods

Illustrations from HIV prevention trials
Groups (clusters) of individuals are randomly allocated to the different treatment conditions. The clusters might be:

- Towns, villages, cities
- Arbitrary geographical zones
- Schools
- Factories
- Clinics, hospitals, medical practices
Why use this design?

- Community-level interventions
- Logistical convenience/acceptability
- Avoid or reduce contamination

Also, for infectious disease interventions
- Capture effects on infectiousness as well as susceptibility
- Capture mass effect of intervening in entire population (indirect as well as direct effects)
Statistical implications of CRT design

- Observations on individuals in the same cluster are *correlated*
- This correlation needs to be accounted for in the *design and analysis*
- Sample size needs to be increased
  - Design effect = $1 + (m - 1) \rho$
  - $m =$ cluster size, $\rho =$ ICC
- Need to use analysis methods that account for correlation
- Imbalance between study arms when small number of clusters
Approaches to analysis

• Analysis of cluster-level summaries
  – Compute summary measure for each cluster: e.g. a risk, rate or mean depending on outcome
  – Compare these cluster summaries between study arms using t-test or non-parametric test

• Regression methods on individual-level data
  – Use random effects models to account for correlation
  – Warning: Not robust when fewer than ~15 clusters per study arm
Example: Cluster-level summaries

- Trial to increase uptake of VMMC in adult men
Example: Cluster-level summaries

<table>
<thead>
<tr>
<th></th>
<th>Proportion aged 25-34</th>
<th>GM of proportions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention clusters (10)</td>
<td>1462/6191</td>
<td>17.7%</td>
</tr>
<tr>
<td>Control clusters (10)</td>
<td>493/3926</td>
<td>13.0%</td>
</tr>
</tbody>
</table>

t-test on log(proportion)
RR: 1.36 (CI: 0.93-1.93)
p = 0.11

Wambura et al, AIDS 2017
Example: Matched pairs CRT

- Mwanza STD trial
- Paired design may help improve balance and reduce between-cluster variance
- 6 pairs of rural communities
- Intervention: improved STD treatment at clinic
- Measured impact on HIV incidence in randomly selected cohort of 1000 adults in each community
- Note: cohort selected from general population, not clinic patients

Grosskurth, Lancet 1995
Example: Matched pairs CRT

- RR computed in each matched pair
- Crude RR computed as geometric mean across pairs
  = 0.57 (CI: 0.42 – 0.76)
- Paired t-test gives $p = 0.004$
- Non-parametric sign test gives $p = 0.03$ (2-sided)
- Note: some imbalance in baseline HIV prevalence
Adjusting for covariates

• Can use 2-stage approach
• Stage 1:
  – Fit regression model to individual data including covariates but NOT study arm
  – Use model to obtain *Expected* number of events (e.g. HIV seroconversions) in each cluster under null hypothesis
  – Compute O/E for each cluster (*ratio residuals*)
• Stage 2:
  – Carry out t-test (paired or unpaired) on the O/E ratio residuals
Adjusting for covariates in paired CRT

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Intervention</th>
<th>Control</th>
<th>Adj RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$O_{i1}/E_{i1}$</td>
<td>$O_{C1}/E_{C1}$</td>
<td>$(O_{i1}/E_{i1})/(O_{C1}/E_{C1})$</td>
</tr>
<tr>
<td>2</td>
<td>$O_{i2}/E_{i2}$</td>
<td>$O_{C2}/E_{C2}$</td>
<td>$(O_{i2}/E_{i2})/(O_{C2}/E_{C2})$</td>
</tr>
<tr>
<td>....</td>
<td>....</td>
<td>....</td>
<td>....</td>
</tr>
</tbody>
</table>

- Adjusting for age, sex and baseline HIV prevalence
- Adj RR = 0.39 (CI: 0.45-0.83)
- Paired t-test gives $p = 0.009$
Limitations of cluster summary methods

These methods have been shown to be highly robust but have a number of limitations:

• They are inconvenient as they generally involve a two-stage procedure
• They give equal weight to each cluster and so are not optimally efficient
• They do not allow the effects of intervention and other covariates (and their interactions) to be estimated together in the same regression model
Individual-level regression methods

- Random effects models and GEE are the most common approaches
- We focus on RE models here

Rates: \[ \log \lambda = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + u_i \]
Binary: \[ \log\text{-odds} = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + u_i \]
Quantitative: \[ \mu = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + u_i \]

where \( \beta_1 \) is intervention effect, \( \beta_2, \ldots \) are covariate effects and \( u_i \) are random cluster effects (representing variation between clusters)
Example: Individual-level regression

- Comparison of two strategies of delivering HPV vaccine to schoolgirls in Tanzania
- Class-based (class 6) vs Age-based (12 years old)
- Primary outcome: HPV vaccine coverage by dose
- 134 primary schools randomly allocated to two strategies
- 3 private schools withdrew leaving 131 (67 class-based, 64 age-based)
- Analysed by Random Effects Logistic Regression
Example: Individual-level regression

<table>
<thead>
<tr>
<th></th>
<th>Age-based</th>
<th>Class-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 1</td>
<td>1788/2180</td>
<td>2896/3352</td>
</tr>
<tr>
<td></td>
<td><strong>82.0%</strong></td>
<td><strong>86.4%</strong></td>
</tr>
<tr>
<td>Dose 2</td>
<td>1695/2180</td>
<td>2808/3352</td>
</tr>
<tr>
<td></td>
<td><strong>77.8%</strong></td>
<td><strong>83.8%</strong></td>
</tr>
<tr>
<td>Dose 3</td>
<td>1572/2180</td>
<td>2639/3352</td>
</tr>
<tr>
<td></td>
<td><strong>72.1%</strong></td>
<td><strong>78.7%</strong></td>
</tr>
</tbody>
</table>

Dose 3
OR = 1.36 (CI: 1.02-1.82)
p = 0.04
ICC = 0.13

Watson-Jones, JID 2012
Summary

- CRTs should be analyzed using methods that allow for correlated data
- Adjustment for covariates is often needed because balance not assured unless large number of clusters
- Regression methods are not robust for CRTs with small number of clusters
- CRTs different from conventional RCTs because study cohorts do not necessarily receive intervention – they are recruited to represent the general population of the community receiving the intervention
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