Methods of analyses for a complex intervention cluster randomised stroke trial – looking for the goose that lays the golden egg

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Aims and objectives

- What is a **cluster randomised trial** (CRT)?
- Principles underlying the analysis of CRTs
- Main **approaches to analyses** of CRTs
- **Case study**: TRACS trial
- **Comparison** of methods
- Discussion

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What is a cluster randomised trial (CRT)?

Cluster randomization trial is trial in which clusters of individuals rather than independent individuals are randomly allocated to intervention groups

Example:
Stroke rehabilitation unit selected as the randomization unit in a trial evaluating complex intervention delivered by multidisciplinary team to caregivers

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Principles underlying the analysis of CRTs

- Methods need to take account lack of independence among individuals in the same cluster
- Intervention effects are measured by **analysing the variation** between cluster-level outcomes

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Main approaches to analysis of CRTs

Based on:

- **Cluster-level** summaries
- **Individual-level** summaries

Cluster-level summaries (1)

Simple

Two-stage approach

Without covariates:

1. **Summary** measure for **each cluster**
2. **Comparison of** two (if 2 treatment arms) **sets** of cluster-specific measures **using an appropriate** statistical **method** (two-sample t-test most common)

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Cluster-level summaries (2)

With covariates:

1. **Individual-level regression** (without the intervention effect) ignoring the clustering of the data. The summary measure for each cluster is the **residual** based on the difference between observed and predicted outcome (if interested in difference as measure of the intervention effect)
2. Comparison of the residuals between the treatment arms

Individual-level summaries

Single-stage approach

Extensions of simpler regression models modified **to allow for** between-cluster variation

Random-effects models – taking account of between-cluster variation, e.g. mixed effects linear regression

Able to estimate **ICC**

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Case study: TRACS

TRAINING CAREGIVERS AFTER STROKE

A pragmatic, multicentre, cluster randomised controlled trial

Aim: to evaluate the clinical and cost effectiveness of a structured, competency-based training programme for caregivers of stroke patients returning home with stroke-related disabilities.

Unit of randomisation: 36 stroke rehabilitation centres

Registered: 928 patients and their caregivers,

Cluster range: 12 to 38 patients

Estimated **ICC**: 0.05

Estimated loss to follow-up: 25%

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Case study: TRACS

TRAINING CAREGIVERS AFTER STROKE

Primary outcome: patient reported NEADL score at 6 months (Nottingham Extended Activities of Daily Living) (0 = Low, 66 = High independence)

Needed **to detect 6 points difference** (patient requiring less help in at least two activities) as clinically relevant

Data available for primary analysis:

678 patients: 330 in intervention and 348 in control

36 stroke rehabilitation centres: 18 in intervention and 18 in control

Primary analysis method: two-level random intercept model with centre covariates as level 2 and patient covariates as level 1

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Methods applied to the TRACS data

Method		Unadjusted analysis	Adjusted analysis	Suitable for CRTs?
Individual-level summaries	Mean diff. (SE) 95% CI p-value **ICC**	0.26 (1.565) (-2.81, 3.33) 0.869 **0.016**	-0.23 (1.336) (-2.85, 2.40) 0.865 **0.027**	✓
Cluster-level summaries	Mean diff. (SE) 95% CI p-value	-0.03 (1.601) (-3.29, 3. 22) 0.984	-0.26 (1.252) (-2.81, 2.29) 0.837	✓
	Mean diff. (SE) 95% CI p-value	**weighted** 0.09 (1.620) (-3.20, 3.38) 0.957		✓
Not considering clustering	Mean diff. (SE) 95% CI p-value	**T-test** 0.27 (1.355) (-2.39, 2.93) 0.843	**Linear regression** -0.22 (1.069) (-2.32,1.87) 0.834	X

Comparison of methods

Cluster-level summaries	Individual-level summaries
Simple (not so if covariates need to be incorporated)	
May not be the most efficient (if clusters of widely varying size)	Cluster weighting is incorporated automatically, so more appropriate if varying cluster size
Two-stages	One-stage, the effects of covariates modelled simultaneously and presented simultaneously with the intervention effects
More robust for small number of clusters	Not robust enough if small number of clusters
	Able to obtain estimates of ICC

Discussion

- Important to **use method allowing for clustering**
- Variety of methods with varying complexity are available for analysing cluster randomised trials
- Even methods allowing for clustering effects can give different results (consider number of clusters, whether cluster size varies)
- A strategy should be developed before any analysis is undertaken to ensure hypothesis-led rather than data driven modelling

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Any questions?

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