

The analysis of an individually randomised
clinical trial of back pain with clustering
effects due to group sessions and repeated
measures

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OVERVIEW

- Design and analysis of individually randomised controlled trials have become increasingly recognised over the last decade or so.
- In a literature review (Bauer et al., 2008) these types of designs are more popular than cluster-randomised and equally popular to the parallel group design

OVERVIEW

- *The design includes patients who are randomly allocated an intervention and:*
 - Both treatment arms are allocated to a group based intervention;
 - One treatment arm is group based and the other a drug;
 - One treatment arm is group based and the other is no treatment.

- *Group-based intervention delivered:*
 - By health professional (e.g. therapist, surgeon)
 - Through a group session (e.g. exercise class or self help group)

CURRENT METHODOLOGY

- The observations on patients are not independent.
- Random effect models used for to take account of the dependence- developed in cluster randomised trials
- Under the null hypothesis, the clustering effect is similar for both arms and therefore pooled over the treatments.
- In individually randomised trial with one grouped based intervention, the clustering effect is likely to differ between arms (Roberts and Roberts, 2005).

CURRENT METHODOLOGY

- Roberts and Roberts (2005) suggest methods based on mixed effects models, which have had limited use
- 87% of studies analysed data completely ignoring clustering effects (Bauer et al., 2008)
- 13% studies analysed data using cluster randomised methods (Bauer et al., 2008)

CURRENT METHODOLOGY (Bauer et al., 2008)

PATIENT(i)	GROUP(j)	TREATMENT	
1	1	Group	
2	1	Group	
3	1	Group	
4	2	Group	
5	2	Group	
6	2	Group	
7	3	Group	
8	3	Group	
9	3	Group	
10	3	Group	
11	4	Individual	
12	5	Individual	
13	6	Individual	
14	7	Individual	} sole member of their own group
15	8	Individual	
16	9	Individual	
17	10	Individual	

CURRENT METHODOLOGY (Bauer et al., 2008)

Homogeneity across the groups (i^{th} patient in j^{th} group)

- At level 1 (patient) we can write: $Y_{ij} = \beta_{0j} + \beta_{1j} \text{treatment}_{ij} + \varepsilon_{ij}$
- At level 2 (group) we can write: $\beta_{0j} = b_{00} + u_{0j}$ $\beta_{1j} = b_{10}$

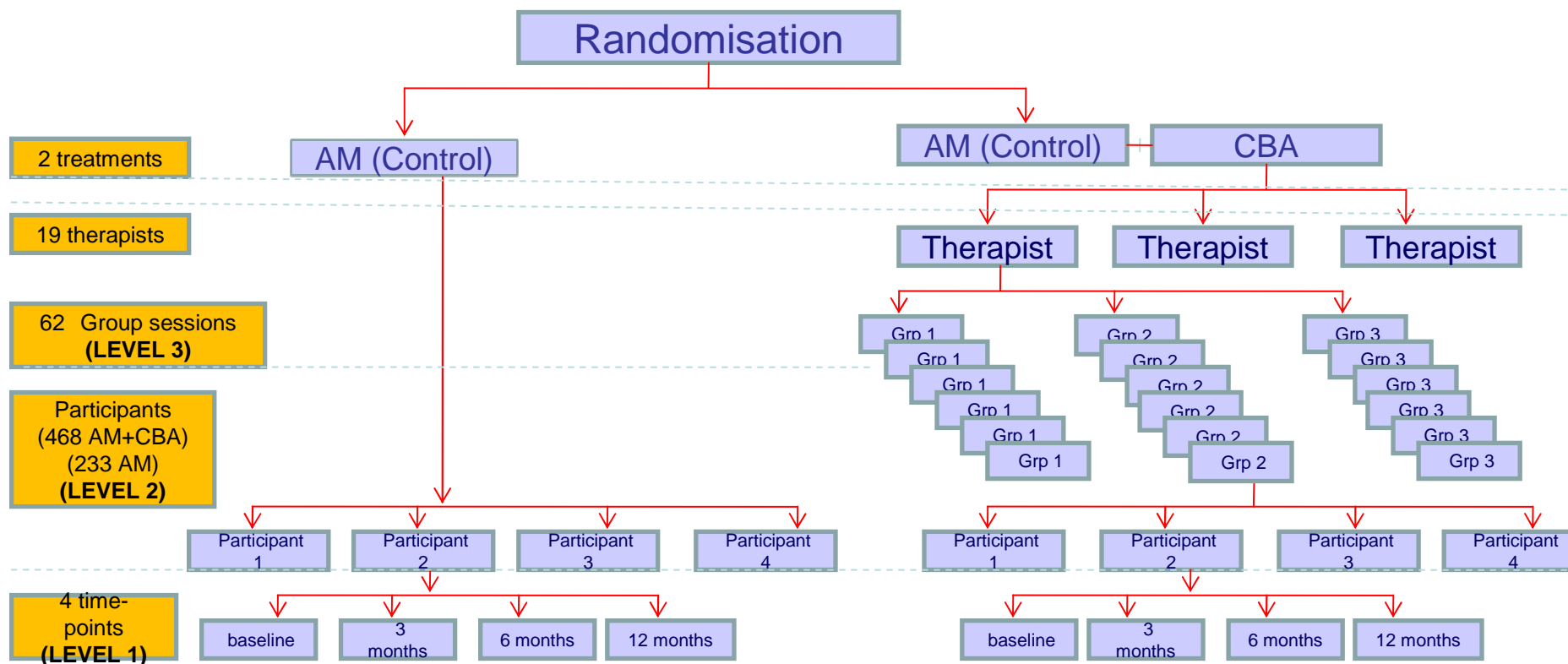
Heterogeneity across the groups

- At level 1 (patient) we can write: $Y_{ij} = \beta_{0j} + \beta_{1j} \text{treatment}_{ij} + \varepsilon_{ij}$
- At level 2 (group) we can write: $\beta_{0j} = b_{00}$ $\beta_{1j} = b_{10} + u_{1j}$

THE AIM OF THIS PRESENTATION

- Take the methodology cited by Bauer (2008) based on multi-level models and develop it in a longitudinal setting using a large clinical trial of back pain (BeST)
- Interventions – active management (AM- control) and AM +CBA (group-based)
- Main outcome– Change from baseline Roland Morris Questionnaire score (0-24)
- Measured at baseline, 3, 6 and 12 months post randomisation
- Participants – 701 participants were randomised

Back Skills Training Trial (BeST)



Multi-level model (with 3 levels)

$$RMQ_{-3m_{tij}} = \beta_o + \beta_1 time_t + \beta_2 treatment_{ij} + \beta_4 time_t \times treatment_{ij} + \epsilon_{tij}$$

Multi-level model (with 3 levels)

Level 1 model (time):

$$RMQ_{-3}m_{tij} = b_{0i/j} + b_{1i/j}time_t + \varepsilon_{tij} \quad (1)$$

Within each group session j and each patient i we derive:

- Intercepts for these patients
- Slopes based on 'TIME' being a continuous variable
- ε_{tij} are the residuals based on the each time t , patient i and group session j
- Different structures will be specified for the variance covariance matrix R_{ij}

$$\varepsilon_{ij} = \begin{pmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \\ \varepsilon_{3ij} \end{pmatrix} \approx N(0, R_{ij})$$

Multi-level model (with 3 levels)

Level 2 model (patient):

$$b_{0i/j} = b_{0j} + u_{0i/j} + b_{2j} \text{treatment}_{ij}$$

$$b_{1i/j} = b_{1j} + u_{1i/j} + b_{3j} \text{treatment}_{ij}$$

where

$$u_{0i/j} \approx N(0, \sigma_{\text{int except: patient (group)}}^2)$$

$$u_{1i/j} \approx N(0, \sigma_{\text{slope: patient (group)}}^2)$$

- From (1)
- the intercept depends on the intercepts specific to the j-th group and the random effects associated with this, accounting from treatment covariate
- The slope associated with time depends on the j-th group and then the random effect associated with this, allowing from the treatment covariate

Multi-level model (with 3 levels)

Level 3 model (group) (HETEROGENOUS EFFECTS OVER TREATMENTS):

$$\begin{array}{lll} b_{0j} = b_0 & b_{2j} = b_{20} + u_{2j} & u_{2j} \approx N(0, \sigma_{slope:group}^2) \\ b_{1j} = b_1 & b_{3j} = b_{31} + u_{3j} & u_{3j} \approx N(0, \sigma_{slope:group}^2) \end{array}$$

- Intercept constant over the groups
- slopes associated with the treatment covariate varies over the groups
- Slopes associates with the treatment and time varies over the groups

Multi-level model (with 3 levels)

$$\begin{aligned}
 RMQ_{-3m_{ij}} = & \beta_o + \beta_1 time_t + \beta_{20} treatment_{ij} + \beta_{31} time_t \times treatment_{ij} \quad \} \text{fixed effects} \\
 & + \underbrace{u_{oi/j}}_{\text{Intercept (level 2)}} + \underbrace{u_{1i/j} time}_{\text{slope (level 2)}} + \underbrace{u_{2j} treatment}_{\text{slope (level 3)}} + \underbrace{u_{3j} treatment \times time}_{\text{slope (level 3)}} + \epsilon_{ij} \quad \} \text{random effects}
 \end{aligned}$$

(1)

NOTE: No intercept random coefficient at level 3 because its assumed to be constant over the group sessions and treatment arms

Multi-level model (with 3 levels)

Reduction of the model – selecting a structure for the random effects

- To preserve the hierarchy
- Test the significance of random effects at level 2 (patient), i.e.

$$H_0 : \sigma_{intercept:i/j}^2 = 0$$

$$H_A : \sigma_{intercept:i/j}^2 > 0$$

$$H_0 : \sigma_{slope:i/j}^2 = 0$$

$$H_A : \sigma_{slope:i/j}^2 > 0$$

Since intercept parameters were significant, we do not test for the random group effects, in order to preserve the hierarchical structure of the data.

Multi-level model (with 3 levels)

Selecting a variance-covariance structure for the residuals

- The distribution of the residuals associates with repeated observation on same patient is:

$$\boldsymbol{\varepsilon}_{ij} = \begin{pmatrix} \varepsilon_{1ij} \\ \varepsilon_{2ij} \\ \varepsilon_{3ij} \end{pmatrix} \approx N(0, R_{ij})$$

- Variance-covariance matrix R_{ij} for the residuals is defined as

$$R_{ij} = \begin{pmatrix} \text{var}(\varepsilon_{1ij}) & \text{cov}(\varepsilon_{2ij}, \varepsilon_{1ij}) & \text{cov}(\varepsilon_{3ij}, \varepsilon_{1ij}) \\ \text{cov}(\varepsilon_{1ij}, \varepsilon_{2ij}) & \text{var}(\varepsilon_{2ij}) & \text{cov}(\varepsilon_{3ij}, \varepsilon_{2ij}) \\ \text{cov}(\varepsilon_{1ij}, \varepsilon_{3ij}) & \text{cov}(\varepsilon_{2ij}, \varepsilon_{3ij}) & \text{var}(\varepsilon_{3ij}) \end{pmatrix}$$

- Different structures for R_{ij} (i.e. unstructured, compound symmetry)

Results

Null (H_0)	Alternative(H_1)	Nested model	Reference model	Change
$\sigma_{slope:i/j}^2 = 0$	$\sigma_{slope:i/j}^2 > 0$	Model1 - $u_{1i/j} = 0$ (REML =8111.06)	Model 1 (REML=8107.59)	5.47 P=0.0009
$\sigma_{intcept:i/j}^2 = 0$	$\sigma_{intcept:i/j}^2 > 0$	Model 1- $u_{1i/j} = 0$ (REML=8111.06)	Model 1 (Infinite likelihood)	-
Constant residual variance $\sigma_{t1}^2 = \sigma_{t2} = \sigma_{t3} = 0$	$\sigma_{t1}^2 \neq \sigma_{t2} \neq \sigma_{t3} \neq 0$	Model 1 with CS (AIC=8111.56)	Model 1 with UN (AIC=8125.6)	-

MODEL	Intercept	Treatment	Time-point	Time -point x treatment
Longitudinal model	2.27 (0.17)	-1.31 (0.28)	0.03 (0.04)	-0.02 (0.06)
Random effects longitudinal model	2.21 (0.19)	-1.26 (0.34)	0.03 (0.02)	-0.01 (0.03)

Conclusion

- The model by Roberts and Roberts (2005) has allowed analysis of partially nested data that better matches the data structure presented in these designs.
- Three-level hierarchy model with time as level 1 (within patient) involve an estimation of a very large number of parameters.
- 'Therapist' could be incorporated into the model as a level 4, in a similar way to 'group session'.
- We can derive the ICCs for patients within group sessions and for group sessions, by adapting the methods cited by Bauer et al (2005) and using the various random components given above.

Thank you !!

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