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

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A primary care-based cognitive behavioural programme for low back pain – the BeST trial

A multicentred randomised controlled trial of a primary care-based cognitive behavioural programme for low back pain. The Back Skills Training (BeST) trial

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Executive summary

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OVERVIEW

- BeST (Back Skills training Trial) with two complex interventions
- In a literature review (Bauer et al., 2008; Roberts and Roberts (2005)) these types of designs are more popular than cluster-randomised and equally popular to the parallel group design.

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CURRENT METHODOLOGY (Bauer et al., 2008)

Intercept Model:

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

Heterogeneity across the groups (each participant is a sole member of his own group in the individual arm)

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

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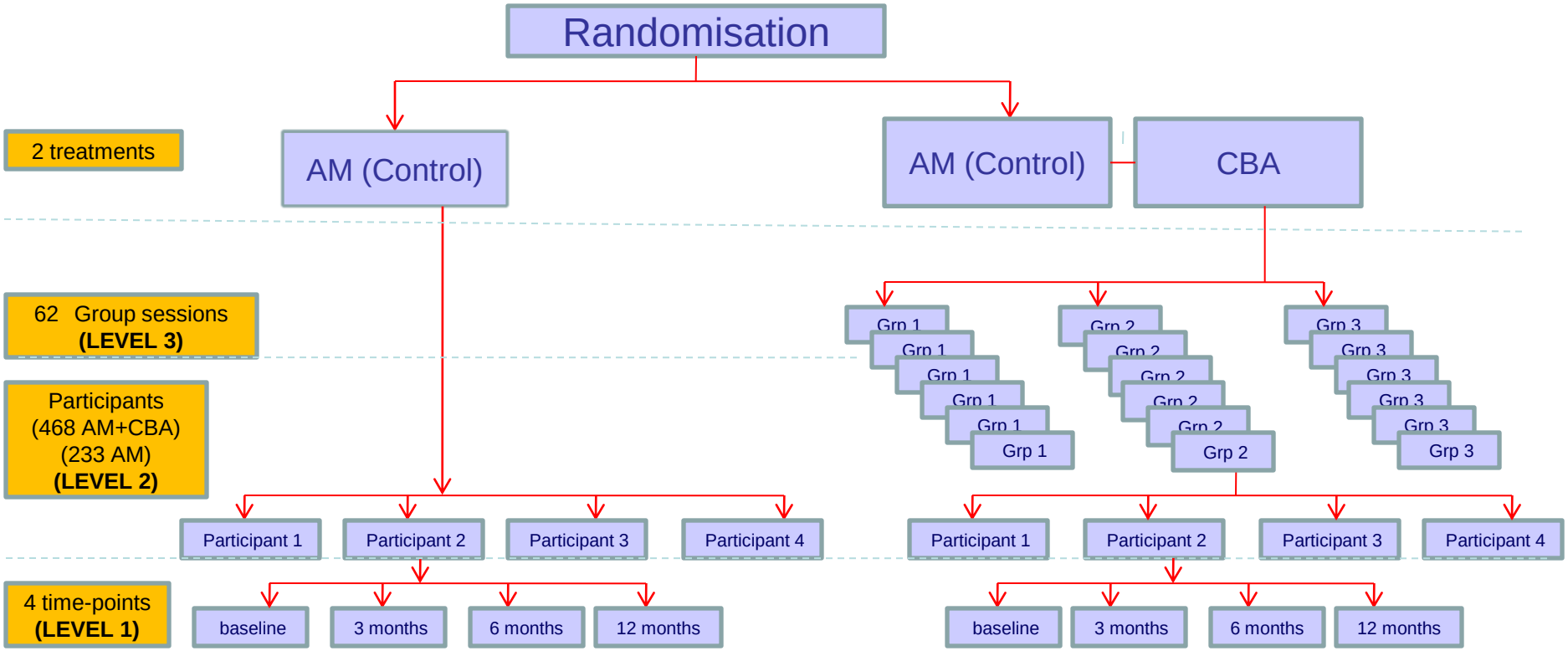
Back Skills Training Trial (BeST)

(701 participants with primary outcome response: ROLAND MORRIS QUESTIONAIRE SCORE)



Multi-level model (with 3 levels)

Level 1 model (time):

$$RMQ_{tij} = \pi_{0ij} + \pi_{1ij} time + \varepsilon_{tij}$$

Time profile for each participant

we derive:

- π_{0ij} are the participant specific intercepts
- π_{1ij} are the time slopes and represent the rate of change for a participant across time
- ε_{tij} are the residuals based on the each time *t*, patient *i* and group session *j*

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:

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

- Variance-covariance matrix R_{tij} for the residuals is defined using unstructured, compound symmetry and autoregressive

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

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Multi-level model (with 3 levels)

Level 2 model (participant) clustering one arm of the treatment

$$\pi_{0ij} = \beta_{000} + \beta_{01j}\,treatment + r_{0ij}\,treatment + \beta_{020}RMQ\_b \qquad r_{0ij} \approx N(0, \sigma^2_{r0ij})$$

$$\pi_{1ij} = \beta_{100} + \beta_{11j}\,treatment + r_{1ij}\,treatment + \beta_{120}RMQ\_b \qquad r_{1ij} \approx N(0, \sigma^2_{r1ij})$$

- β_{000} overall mean RMQ score over time for all participants in the AM arm
- β_{01j} difference in the mean RMQ for group j, within AM+CBA arm and the overall mean in AM arm
- r_{0ij} the random departure from the overall difference for every participant in his group
  is the fixed baseline RMQ parameter

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Multi-level model (with 3 levels)

Level 3 model (group) clustering one arm of the treatment

$$\beta_{000} = \gamma_{000} \qquad \beta_{01j} = \gamma_{010} + u_{01j} \qquad \beta_{020} = \gamma_{020} \qquad u_{01j} \approx N(0, \sigma^2_{u01j})$$

$$\beta_{100} = \gamma_{100} \qquad \beta_{11j} = \gamma_{110} + u_{11j} \qquad \beta_{120} = \gamma_{120} \qquad u_{11j} \approx N(0, \sigma^2_{u11j})$$

- γ_{000} overall mean RMQ score for all participants in the AM arm (as before)
- γ_{010} difference between the overall treatment mean
- u_{01j} is the deviation of each group mean from this mean in the AM+CBA arm

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Multi-level model (with 3 levels)

$$RMQ_{tij} = \gamma_{000} + \gamma_{100} time + \gamma_{100} treatment_{ij} + \gamma_{020} RMQ +$$
$$\gamma_{110} time * treatment + \gamma_{120} time * RMQ + \quad \text{fixed}$$

$$r_{0ij} treatment + r_{1ij} treatment * time +$$
$$u_{01j} treatment + u_{11j} treatment * time + \quad \text{random}$$
$$\varepsilon_{tij}$$

Multi-level model (with 3 levels)

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

- RANDOM EFFECT : To preserve the hierarchy test the significance of random effects at level 2 using change in REML , i.e.

$$H_0 : \sigma^2_{r1ij} = 0 \qquad H_A : \sigma^2_{r1ij} > 0$$

$$H_0 : \sigma^2_{u11j} = 0 \qquad H_A : \sigma^2_{u11j} > 0$$

- FIXED EFFECT : Test the significance of the fixed terms using change in -2 Max LL

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Results

NULL(H_0)	ALTERNATIVE (H_1)	NESTED MODEL	REFERENCE MODEL	CHANGE
$\sigma^2_{r1ij} = 0$	$\sigma^2_{r1ij} > 0$	Model1 – $r_{1ij} = 0$ (REML =8063.4)	Model 1 (REML=8063.4)	Negligible
$\sigma^2_{u11j} = 0$	$\sigma^2_{u11j} > 0$	Model 1- u_{11j} = Model 2 (REML=8063.8)	Model 1- r_{1ij} (REML=8063.4)	0.4 P=0.2635
$\gamma_{110} = 0$ Treatment* time	$\gamma_{110} \neq 0$	Model 2- γ_{110} =Model 3 (ML=8038.4)	Model 2 (ML= 8035.7)	2.7 P=0.0502
$\gamma_{120} = 0$ Treatment*baseline	$\gamma_{120} \neq 0$	Model 4 (ML=8038.4)	Model 3- γ_{120} =Model 4 (ML=8038.4)	Negligible
$\sigma^2_{t1} = \sigma^2_{t2} = \sigma^2_{t3} = 0$ Constant residual variance	$\sigma^2_{t1} \neq \sigma^2_{t2} \neq \sigma^2_{t3} \neq 0$	Model 4: CS (AIC=8066.2) Model 4 with UN (AIC=8052.5) Model 4: AR (AIC = 8057.3)		

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Multi-level model (with 3 levels)

$$RMQ_{tij} = \gamma_{000} + \gamma_{100} time + \gamma_{100} treatment_{ij} + \gamma_{020} RMQ + \Big\} \text{ fixed}$$

$$r_{0ij} treatment + u_{01j} treatment + \varepsilon_{tij} \Big\} \text{ random}$$

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Results

MODEL	*Intercept*	*Baseline RMQ*	*Mean Treatment difference*	*Time-point*	*P-value for mean treatment difference*
Longitudinal model	-0.46 (0.32)	0.78 (0.03)	1.24 (0.30)	0.028 (0.15) 0.04 (0.15)	0.0001
Random effects longitudinal model	-0.11 (0.33)	0.76 (0.03)	1.21 (0.30)	0.15 (0.02)	0.0001

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Conclusion

- Power of the study is important in fitting these model
- Results of the longitudinal analysis and hierarchical model very similar

- ***FOOD FOR THOUGHT:***
- Implication of clustering effects → increase sample size → more patients to recruit
- If clustering effects are negligible, then (a) is it right to spend large amounts of tax-payers recruiting more patients and (b) and therefore is it ethical to randomise more patient unnecessarily into trials?

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