

Statistical Issues in The Analysis of Non-pharmacological Therapy Trials With Clustering by Care-provider or Therapy Group

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Non-Pharmacological Intervention Trials

Trials of treatments involving “activities” by a health care provider

Examples

- Talking therapies such as counselling or cognitive behavioural therapy.
- Physical therapies such as Physiotherapy for musculoskeletal disorders (e.g. back pain).
- Speech therapy.
- Surgery.

Overview of Presentation

- An example - The PRIDE trial
- Therapist and Trial Designs
- Statistical Modelling Issues
- Clustering & Heterogeneity
 - Nurse Practitioner Trial
- Multiple Care Providers per Patient
 - The ADAPT Trial
 - Simulation study for Multiple Care Providers per Patient
 - Sample size

PRIDE: Pilot Randomised Controlled Trial of collaborative care for the management of depression in the elderly. Chew Graham, Lovell, Roberts et al British Journal of General Practices (2007)

Participants

- 105 people aged 60 or older where randomised to collaborative care or usual care.

Intervention & Methods

- The intervention group received care managed by **a** community psychiatric nurse who delivered an intervention comprising a facilitated self-help programme using a treatment manual (Six face to face session followed by 5 phone sessions).
- A nested qualitative study explored the views of patients and health professionals regarding the acceptability and effectiveness of the intervention.

Results

- At 4 months intervention group less likely to depressed (20%, 9/45) than the control (40%, 17/43) (Adjusted odds ratio 0.32, 95% c.i. 0.11 to 0.93, $p = 0.036$)

PRIDE Trial: Implications for Precision

- Whilst the trial involved 105 patients, the intervention delivered by just one care provider.
- If we wish to generalize to other care provider drawn from the same population, we need to capture variation in outcome between care providers as well as patients.
- Precision of odds ratio does not include between care-provider variation.

PRIDE Trial: External Validity

Intervention was delivered by psychiatric research nurse specially recruited to deliver the trial intervention.

Patient interview

“I couldn’t fault him in any way. He was brilliant with me.”
(ID 42)

Patient interview

“I found him a very nice chap. He was somebody that you could have a conversation with...” (ID 55)

Therapist Variation and Clinical Trials

Outcome for patients treated by the same therapist may be more similar than outcomes for patients treated by different therapists due to therapist characteristics such as:

- Experience
- Training
- Competence
- Alliance

This variation between therapist has implications for the Precisions of therapy trials analogous to cluster randomised trials

- Patients are clustered by care-provider.
- Multilevel analysis/Multilevel modelling
- Larger sample size.

Also implications for internal and external validity

Consort Guidance for Non-pharmacological Trials

Consort Guidelines for Non-pharmacological Treatment Trials has drawn attention to the issue. (Boutron et al *Annals of Internal Medicine* 2008)

They recommend that trial of Non-pharmacological Treatment reports how clustering by care provider has been considered in relation to:

- Selection of care providers.
- Sample size calculation.
- Allocation of care providers to each trial arm.
- Statistical analysis of outcome.

Group Administered Treatments

- Example Interventions: Group Cognitive Behavioural Therapy(CBT), Exercise Classes for Rehabilitation, Substance misuse support groups.
- Outcome may be more similar for subjects in the same class or group as patients may interact , which may also be a component of the treatment.
- The clustering effect of group delivery only applies to group therapy arm if trial patients are randomised individually.
- Each therapy group may be considered as a cluster.

Design and analysis of trials with care-provider variation

Type of Comparisons involving Care Providers

- **Techniques**

Different treatment methods delivered by the same type of care provider.

- *Face-2-Face* and *Telephone* delivered CBT therapy for patients with OCD.

- Different surgical procedures.

- **Care Provider Characteristics**

Same treatment but different types of care-provider.

- Comparison of nurse practitioners and general practitioners in primary care.

- **Packages**

Different techniques and different characteristics combined.

- CBT delivered by a clinical psychologist with Non-directive counselling delivered by a counsellor.

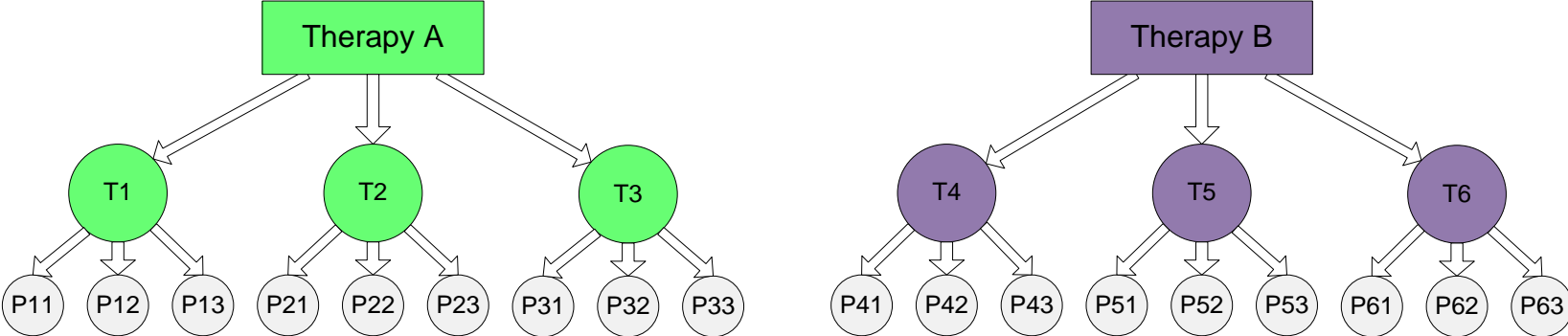
[see Walwyn & Roberts SMMR 2009]

Trial Designs for Therapist Treatment

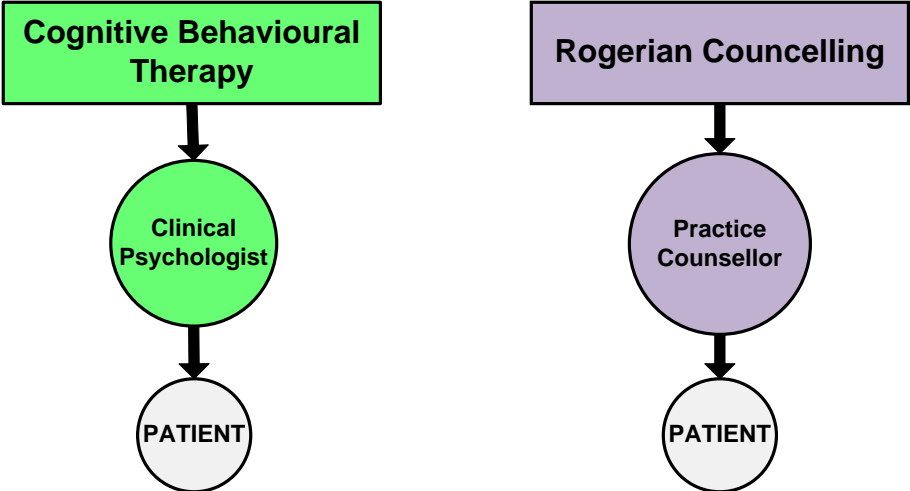
- Nested (Therapist) Design also called Hierarchical (Therapist) Design.
 - Comparison of two chiropractic manipulation with physiotherapy
- Partially Nested (Therapist) Design.
 - Comparison of physiotherapy with an information booklet
- Crossed (Therapist) Design also called a Stratified (Therapist) Design.
 - Comparison of surgical procedures with the all surgeons delivering both procedures

Nested Therapist Design also called Hierarchical Design

Schematic Unit Diagram

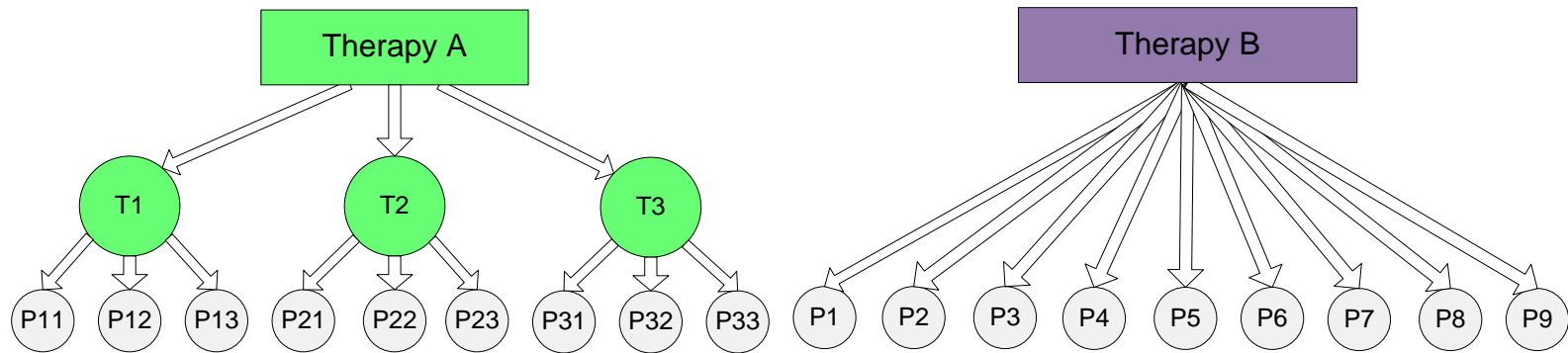


Treatment Classification Diagram

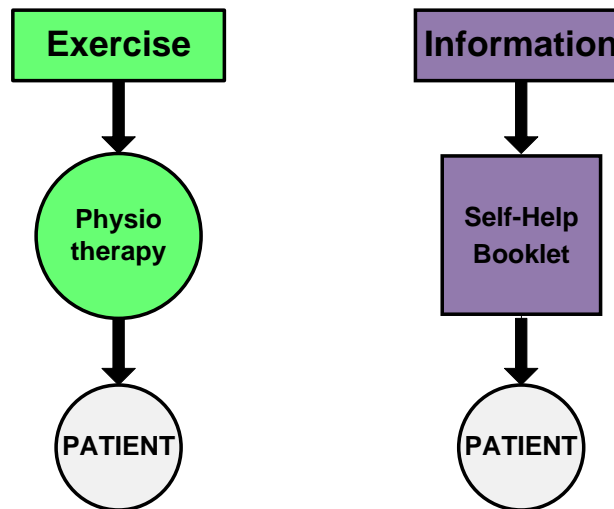


Partially Nested Therapist Design

Schematic Unit Diagram

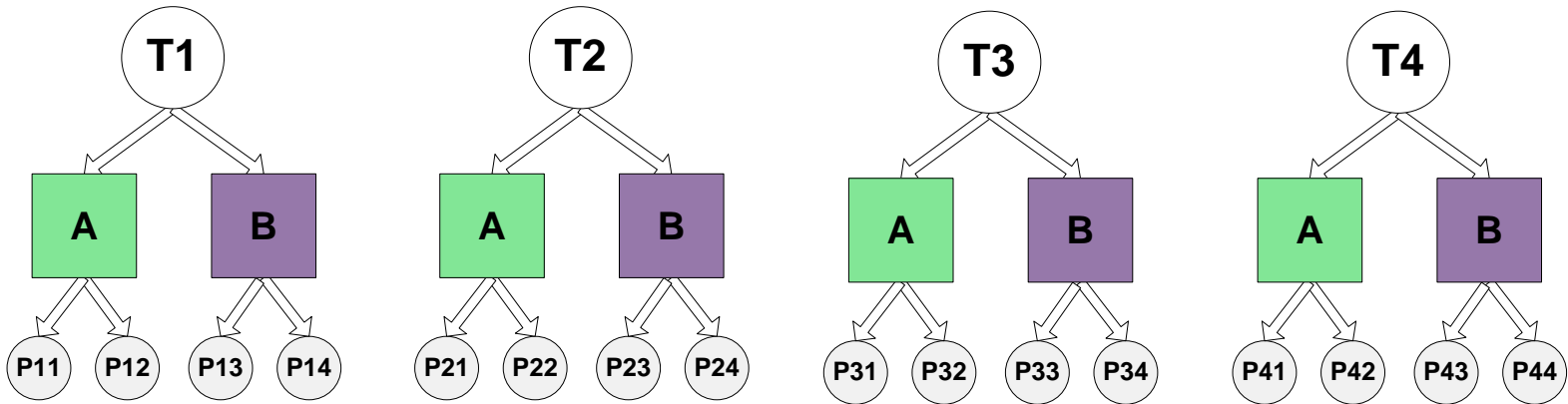


Treatment Classification Diagram

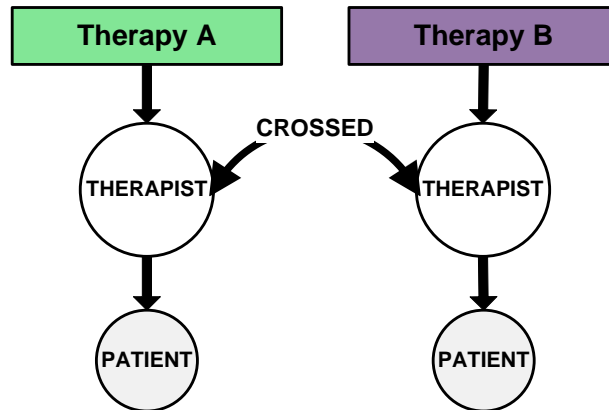


Crossed Therapist Design

Schematic Unit Diagram



Treatment Classification Diagram



Statistical Analyses for Nested and Partially Nested Designs

- Statistical analysis of Nested and Partially nested designs are similar to cluster randomised trials.
- There is nevertheless added complexity due to the cluster being defined by treatment rather than randomisation.

Comparison of Cluster Randomised, Therapist & Group Therapy Trials

<i>Trial Type</i>	<i>Cluster Randomised Trial</i>	<i>Nested Therapist Trial</i>	<i>Group Therapy Trial</i>
<i>Randomisation</i>	Cluster	Individual / Cluster	Individual / Cluster
<i>Between Cluster Variation</i>	Same in both arms	May differ between arms	May differ between arms
<i>Cluster Size</i>	Similar due to randomisation	May differ between arms	May differ between arms
<i>Cluster Membership</i>	Defined at randomisation	May be poorly defined	Should be well defined for closed group treatments
<i>Validity Concerns</i>	Selection of patients within clusters	Selection of therapist for treatments	Selection of therapist for group treatments

Statistical Analyses for Nested and Partially Nested Designs

Additional complexity due to clusters being defined by treatment

- Between Arm Heterogeneity
- Multiple therapists or groups per patient
- Non-compliance

Between Arm Heterogeneity and Clustering

An Example of Heterogeneity of Clustering

RCT comparing Nurse Practitioners with General Practitioners for acute primary care (Venning et al BMJ 2000)

- 20 nurse practitioners seeing a mean of about 30 patients (range 30 to 36)
- 71 general practitioners seeing a mean of 8 patients (range 2 to 29)

Outcome measures:

- Patient satisfaction
- Consultation process (length of consultation, examinations, prescriptions, referrals),
- Health service costs

Multilevel Models for Nested Therapist Design

Statistical analysis can be based on a multilevel models with patients at level 1 and therapist or therapy group at level 2.

Random Intercept Model

$$y_i = \alpha + \delta t_i + u_{therapist(i)}^{(2)} + \varepsilon_i^{(1)}$$

Treatment Effect Therapist (or Group) Variation Patient Variation

Heteroscedastic Model

$$y_i = \alpha + \delta t_i + u_{therapist(i)}^{(2)} (1 - t_i) + v_{therapist(i)}^{(2)} t_i + \varepsilon_i^{(1)} (1 - t_i) + \zeta_i^{(1)} t_i$$

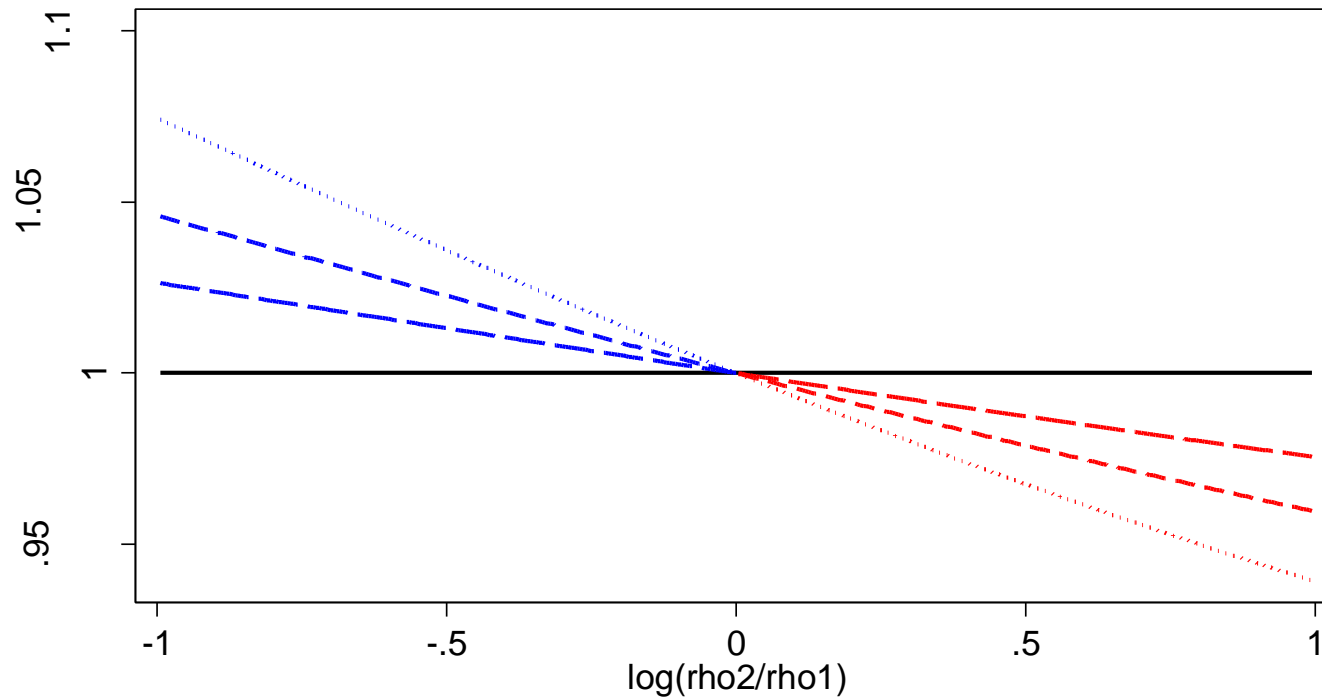
NP-GP Trial

Treatment Effect- Patient Satisfaction

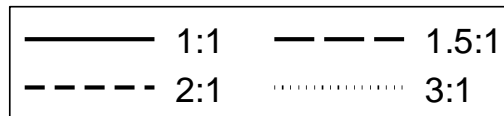
Models	Treatment					
	Effect	SE	p	ICC	95% c.i.	
OLS	0.19	0.028	<0.001	-	-	-
Random Intercept	0.21	0.048	<0.001	$\rho_{pool}=0.095$	(0.049 to 0.148)	
Hetero-Scedastic	0.21	0.042	<0.001	$\rho_{NP}=0.044$	(0.005 to 0.096)	
				$\rho_{GP}=0.111$	(0.044 to 0.181)	

Choice of model effects treatment effect standard errors

Implications of assuming Homogeneity when clustering differs between arm.



Ratio of cluster sizes between arms (m2:m1)



Geometric Mean cluster size =20 , Geometric Mean ICC =0.05

Conclusions: Clustering and Heteroscedasticity

- In Cluster Randomised Trials heteroscedasticity of ICC not important.
[see Korendijk et al Methodology (2008) for simulation study]
- In Nested Therapist Trials cluster size and intra-cluster correlation may be an important issue - should be modelled if cluster sizes differ systematically between treatment arms
- Important also to consider differences in total variance between treatment especially in partially nested designs. [see Roberts & Roberts]

Treatments with Multiple Care Providers per Patient

The ADAPT Trial for the Treatment of Moderate to Severe Depression in Adolescents

Participants: 208 adolescent presenting with moderate to severe depression.

Interventions:

- Medical Management (SSRI)
 - Cognitive-Behaviour Therapy (CBT) + Med. Man. (SSRI)
- CBT delivered by 15 therapists

Primary Outcome measure: HoNOSCA at 3 & 6 months

Secondary measures: CDRS, MFQ

Design: Partially Nested

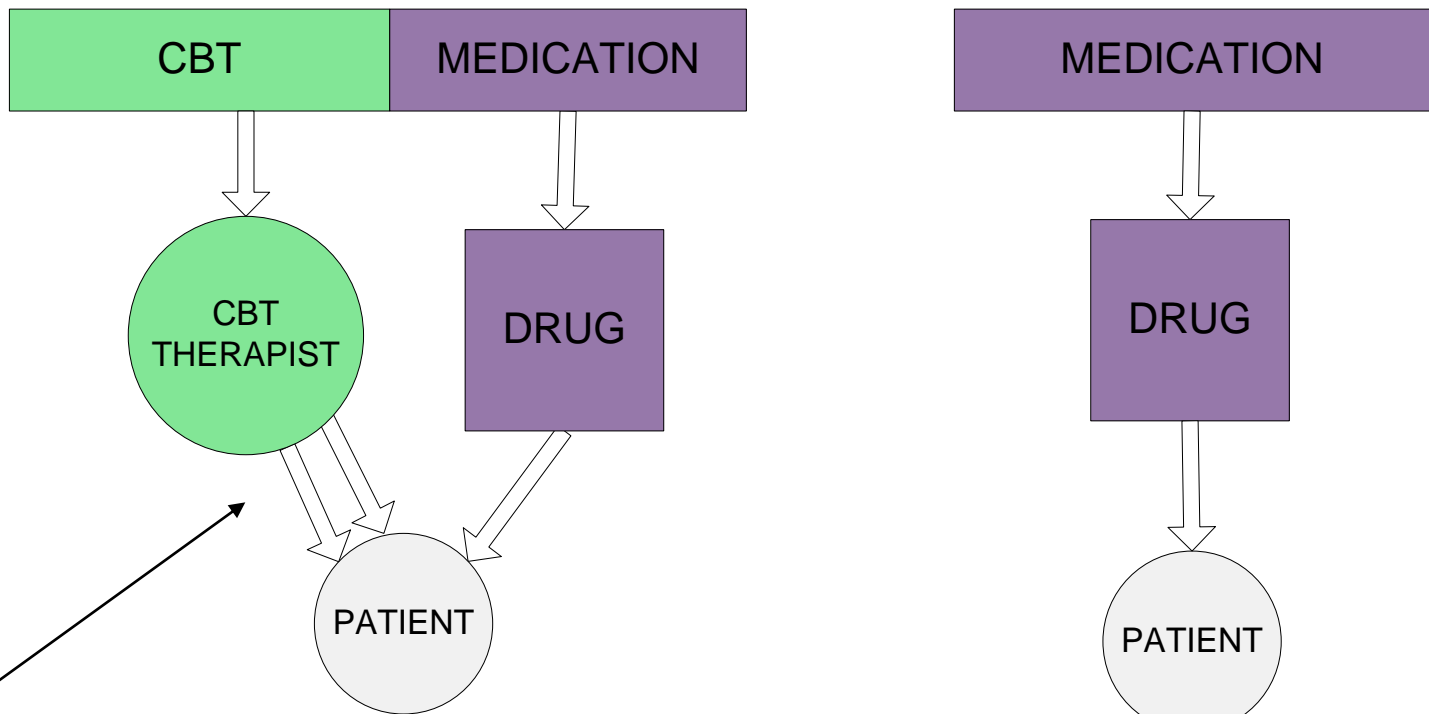
ADAPT: Trial Case Load for CBT

Patients per CBT Therapist	Freq
29	1
27	1
9	2
8	1
5	1
3	3
2	4
1	3
No therapy/ missing therapist id	2

CBT Therapists per patient	Freq
0	2
1	91
2	12

ADAPT Trial: Treatment Classification Diagram

Some Patients receive treatment from more than one CBT therapist



Multiple Membership

Statistical Analysis Options

- Receipt of treatment from more than one therapist creates a multiple-membership relationship.
- This conflicts with the hierarchy of standard multilevel models.

Options for analysis

1. Define a “primary” therapist
(giving most sessions or treatment)
Analyze by primary therapist using hierarchical models described above.
2. Fit a multiple-membership model.

Multiple Membership Model for Therapist or Open Groups

$$y_i = \alpha + \delta t_i + \sum_{j \in \text{therapist}(i)} w_{ij} u_j^{(2)} + e_i^{(1)}$$

Treatment Effect

Proportion of time i^{th} patient receives treatment from therapist

Random Effect for j^{th} Therapist or Group

Patient Variation

Assume $\sum_{j \in \text{therapist}(i)} w_{ij} = 1$

Variances of the random effects u_j constrained to be equal.
Covariance's of the u_j constrained to be equal 0.

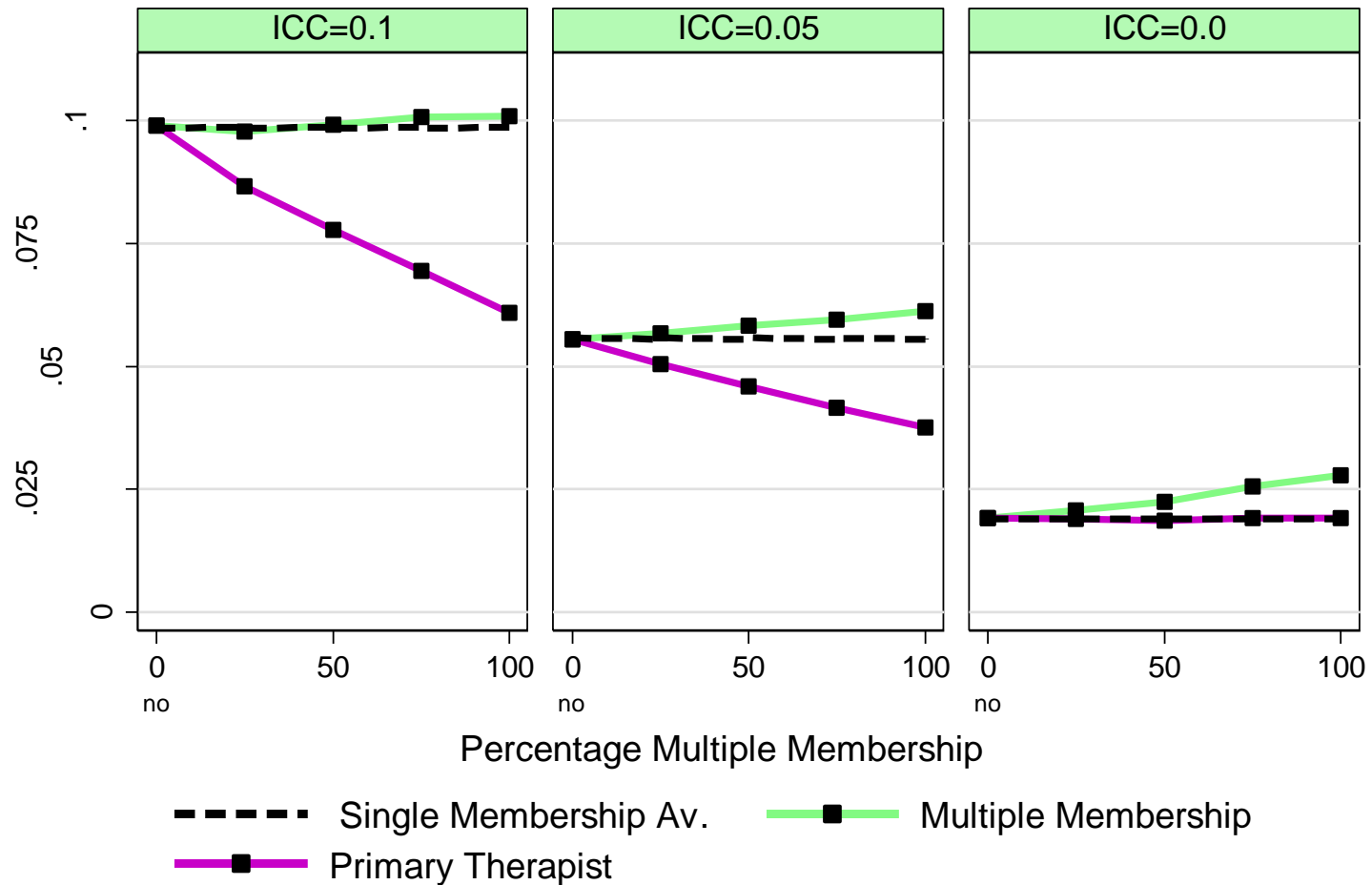
ADAPT: Treatment Effect Estimates for the *Health of the Nation Outcome Scale for Child & Adolescents (HoNOSCA)* at 6 months

	Treat. effect*	SE	ICC	Design Effect
OLS (assuming no clustering)	1.12	1.11		
<u>Primary Therapist</u> Prim. CBT Therapist	1.00	1.31	0.060	1.38
<u>Multiple Membership</u> CBT Therapist	0.86	1.41	0.103	1.61

* Adjusted for Age, Gender, Site and baseline HoNOSCA.

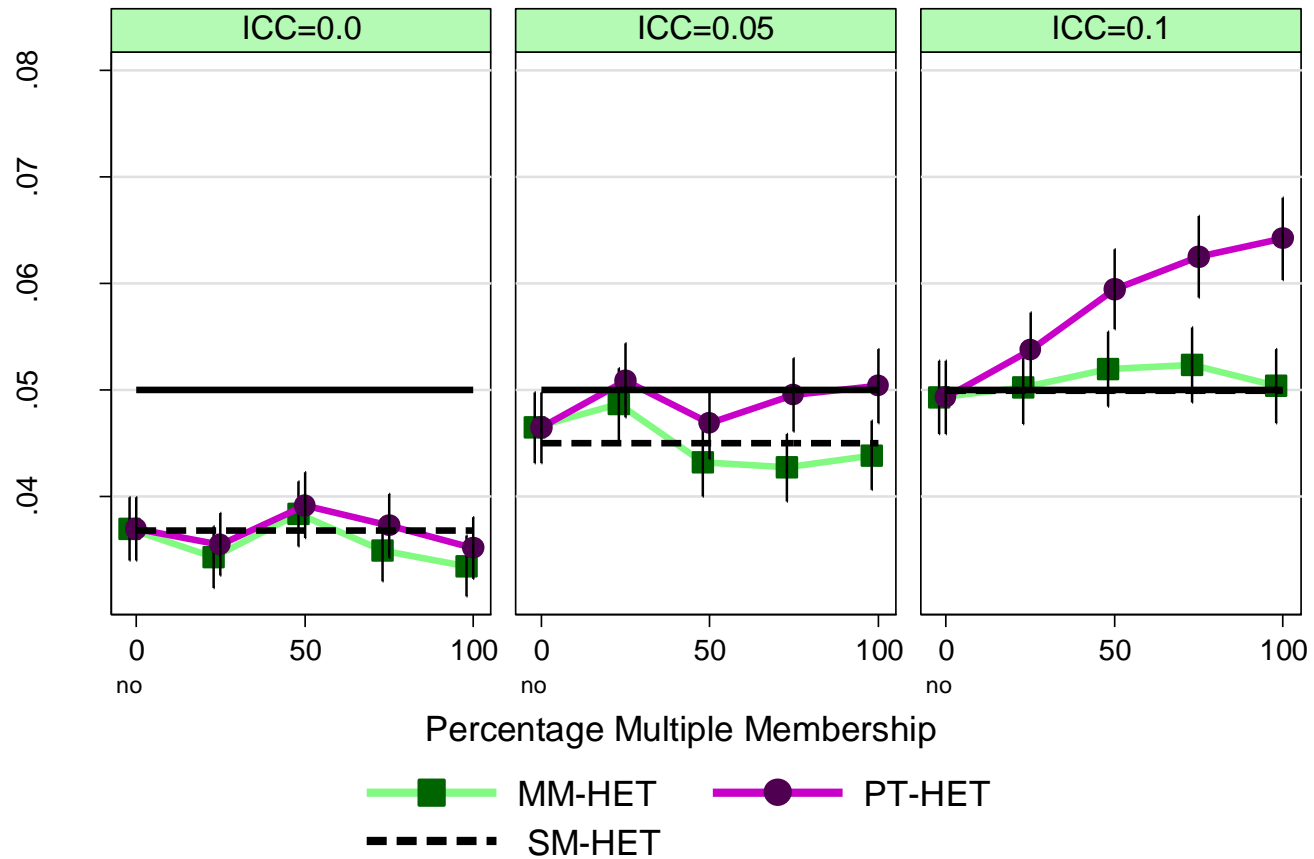
• Analysis carried out using STATA.

Simulation results - ICC



Graphs by icc

Simulation results - Test size



Graphs by ICC Simulated

Sample Size Implications of Multiple Membership Models

Design Effect and Multiple Membership

Single Membership with Equal cluster size

$$\text{Design Effect} = 1 + (m - 1)\rho$$

Multiple Membership

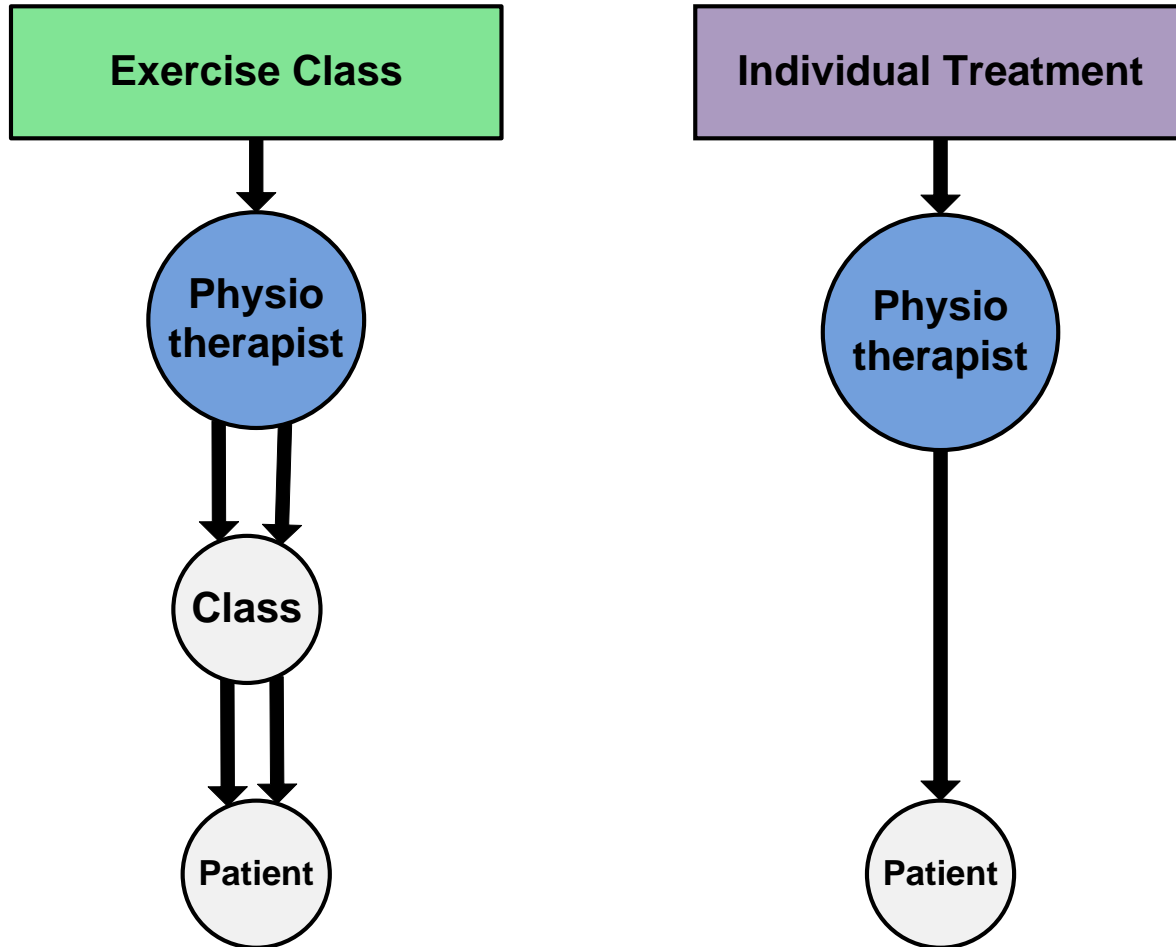
Define $w_j = \sum_i w_{ij}$ the total contribution of the j^{th} therapist or group

$$\text{Design Effect} = 1 + \left(\bar{w} + \frac{\sigma_w^2}{\bar{w}} - 1 \right) \rho \quad \longleftarrow \quad \text{Intra-Cluster Correlation } (\rho)$$

$$\text{where } \bar{w} = E[w_j] \quad \text{and} \quad \sigma_w^2 = \text{Var}[w_j]$$

The design effect relates to the numbers of “whole time” treatment per therapist or the number of whole time treatment per group.

Trials with more complex patterns of clustering



Summary – Multiple therapists/Open groups

Analysis

- Where patients receive treatment from multiple care-provider multiple membership models should be considered.
- Simple multiple membership models can be fitted in STATA.
- No major problems with convergence.
- More complex models fitted in ML-Win.

Sample size

- Sample size depends on the numbers of “whole time” patients per care provider or the number of “whole time” patients per group.

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CLSAMPST - Stata Routine for Calculating Sample Size

- Stata routine for calculating Sample Size and Power for Nested and Partially Nested Designs.
- Calculates power using Satterthwaite or normal approximation.
- Numerical search to find sample size working from normal approximation.
- Can allow for variable cluster size.
- Binary outcomes using normal approximation.

Available from

www.medicine.manchester.ac.uk/healthmethodology/research/biostatistics/data/clsampst/