



Design and analysis of randomised trials with treatment-related clustering

Dr Rebecca Walwyn

Clinical Trials Research Unit

Leeds Institute for Clinical Trials Research

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LSHTM Centre for Statistical Methodology



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Acknowledgements

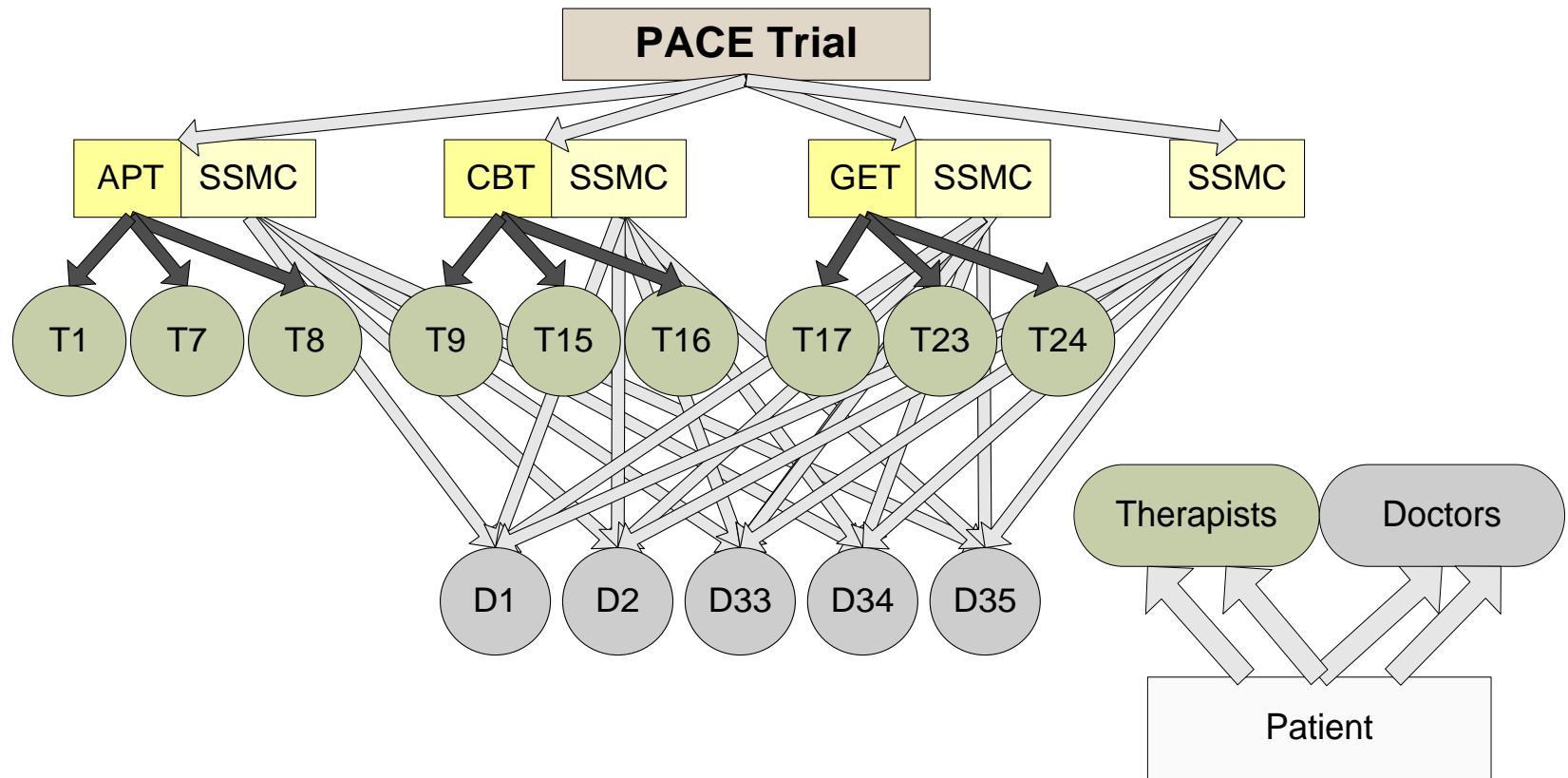
- PhD was funded by a Medical Research Council Special Training Fellowship in Health Services and Health of the Public (ref: G0501886) between 2006 and 2010, supervised by Chris Roberts in Manchester.
- Walwyn R, Roberts C. Therapist variation in randomised trials of psychotherapy: Implications for precision, internal and external validity. *Statistical Methods for Medical Research*, 2010, **19**, 291-315
- Roberts C, Walwyn R. Design and analysis of non-pharmacological treatment trials with multiple therapists per patient. *Statistics in Medicine* 2013; **32**:81–98.
- Walwyn R, Roberts C. Meta-analysis of absolute mean differences from randomised trials with treatment-related clustering associated with care providers. *Statistics in Medicine* 2015; **34**:966–983.
- Walwyn R, Roberts C. Meta-analysis of standardised mean differences from randomised trials with treatment-related clustering associated with care providers. *Statistics in Medicine* 2017; **36**:1043–1067.



Overview

- Motivating Example
- Historical Background
- Research Questions
- Trial Designs
- Implications for Precision
- Implications for Internal Validity
- Implications for External Validity
- Conclusions
- Ongoing and Planned Further Research

Motivating Example



Therapists are nested (APT, CBT, GET; not SSMC)

Doctors are crossed with medical care (SSMC)

White *et al* (2011) *Lancet*, **377**(9768): 823-836

Historical Background

- The intervention of interest in a psychotherapy trial broadly lies ‘**somewhere in the therapist and his behavior**’ (Kiesler, 1966, p128)
- The notion that patient outcomes vary between therapists has been recognised by psychotherapy researchers and clinicians **since the origin of the field** (Wampold, 2001).
- Methods for studying the contribution of therapists to patient outcomes have **changed over time**.
- Despite awareness of therapist variability, the **statistical and wider conceptual implications** of therapist variation for psychotherapy trials have not been widely recognised.
- The clustering implications of therapist variability were outlined firstly within the psychotherapy literature by **Martindale (1978)** and then by **Crits-Christoph and Mintz (1991)**.
- Subsequently **Roberts (1999)**, **Lee and Thompson (2005)** and **Roberts and Roberts (2005)** have brought the issue to the attention of the mainstream medical statistical community.

What is therapist variation in psychotherapy trials?

- It is the result of therapists being **an important component** of the intervention separate to but interacting with their behaviours

Psychotherapy = Therapist + Behaviours + Interaction

- The therapist is a random treatment variable: “patient outcomes may vary systematically by therapist”
- Their behaviours (or the ‘theoretical orientation’ of the therapy) are often a fixed treatment variable
- Hence, “*treatment-related clustering*”

Research Questions

<i>Example:</i>		Techniques	
		Counselling	Advice
Therapists	Counsellors	A	B
	GPs	C	D

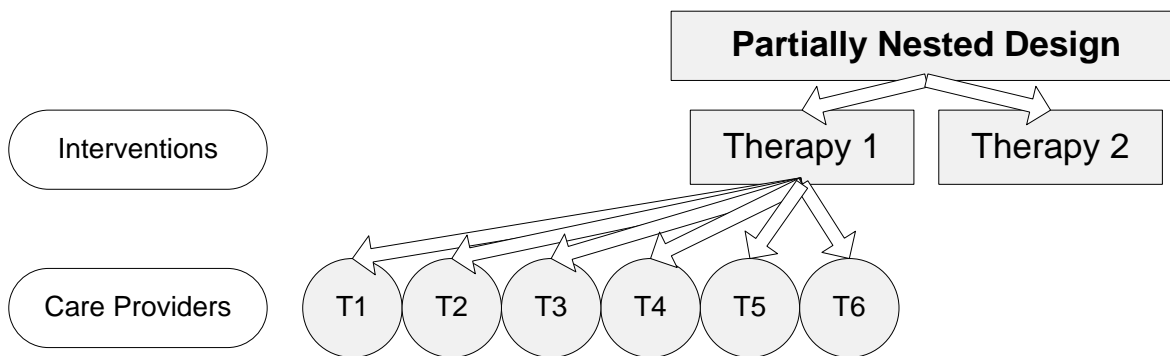
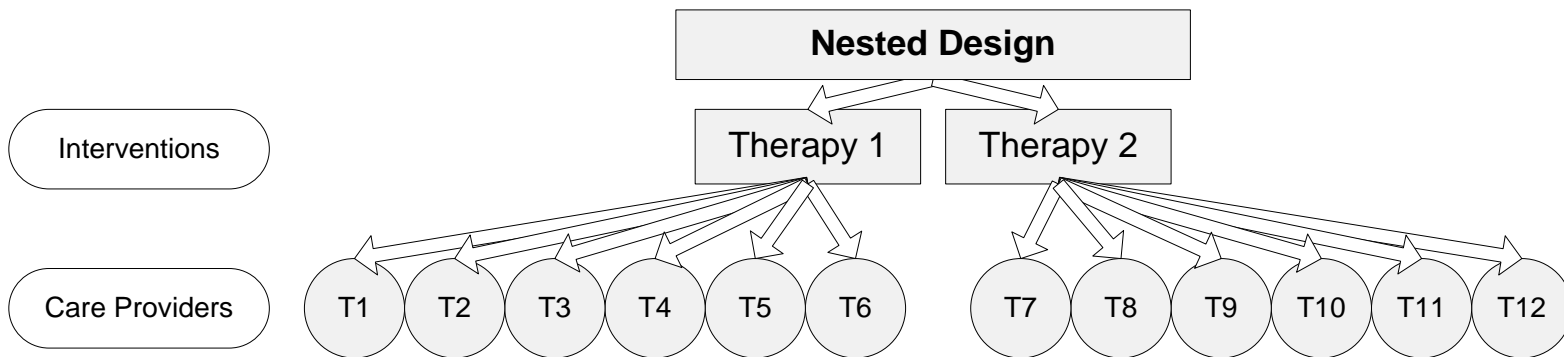
1. Techniques
 2. Therapist characteristics
 3. Packages
- } "Complex" Interventions

Trial Designs

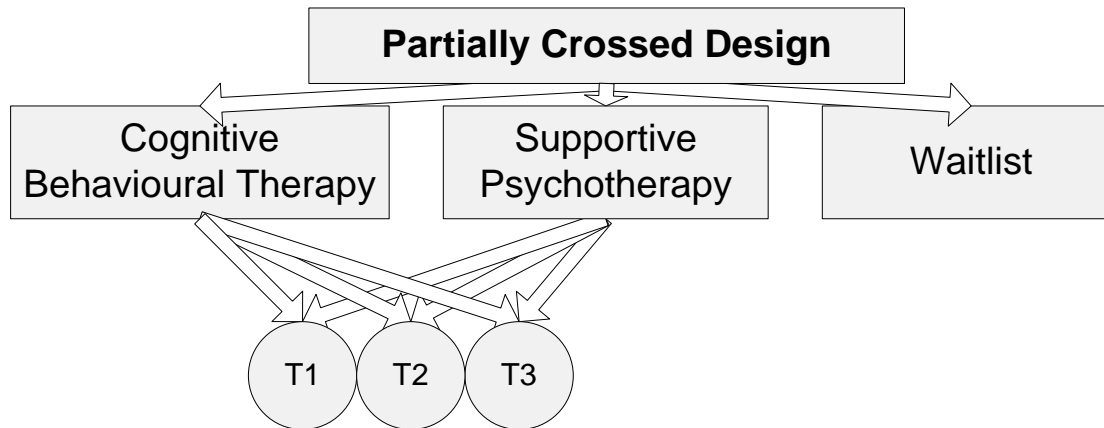
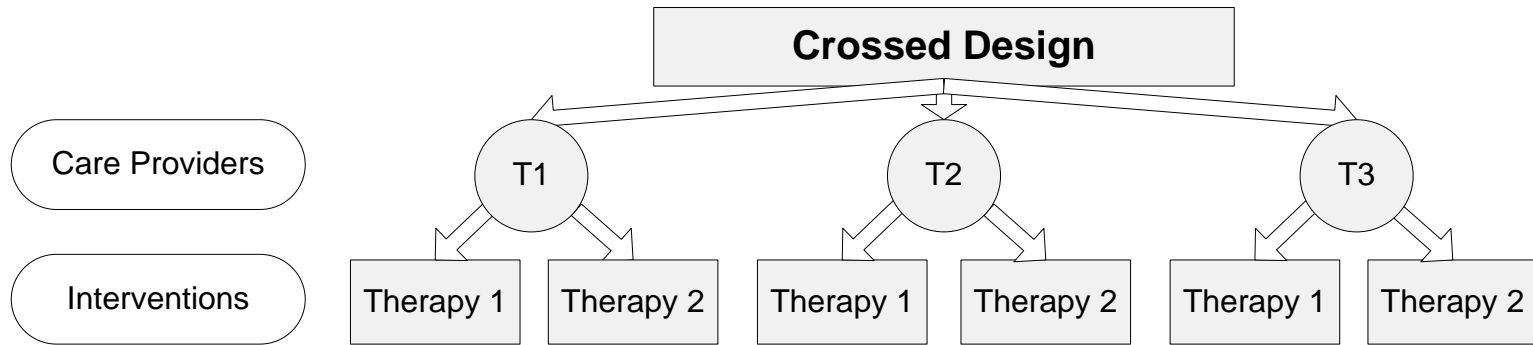
- Due to “therapists” being distinct from “behaviours”, in addition to the relationship between behaviours and patients, there are a further two relationships that need to be considered and reported:
 - Relationship between behaviours and therapists
 - Relationship between therapists and patients
- These relationships describe the data structure, which should inform the sample size calculation and method of analysis.
- In psychotherapy, behaviours are synonymous with treatments.
 - In my view, behaviours and therapists are two components of a complex intervention, each being represented by a separate “treatment variable” (plus the interaction between them). However, there is a need to standardise the terminology used.



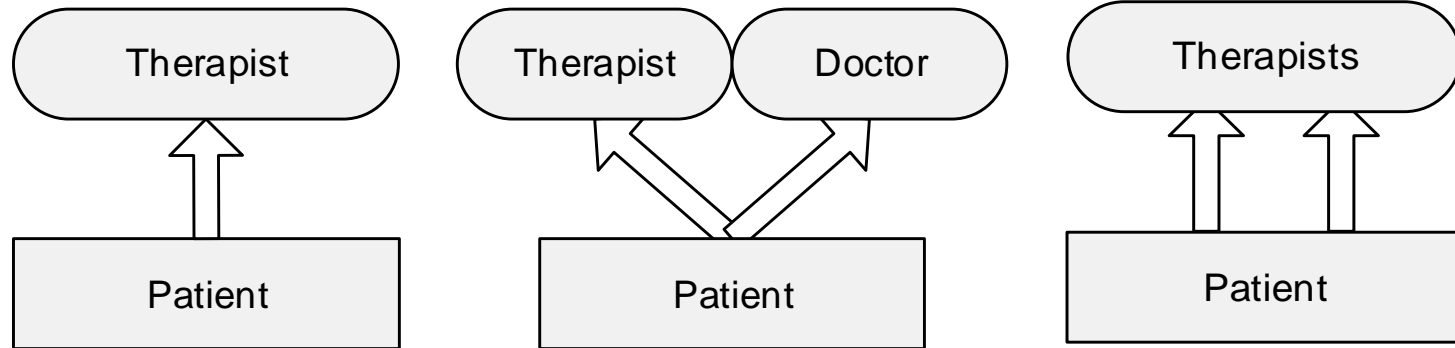
Trial Designs – Interventions and Care Providers (1)



Trial Designs – Interventions and Care Providers (2)

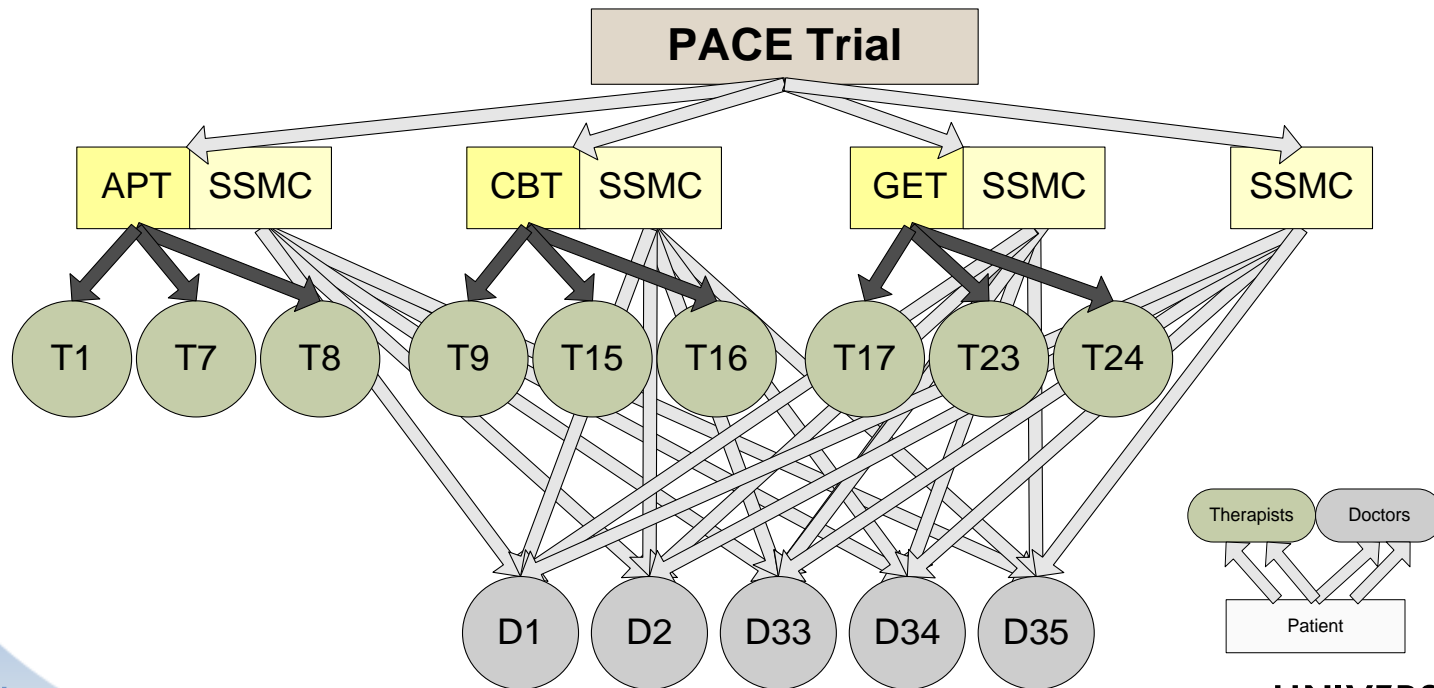
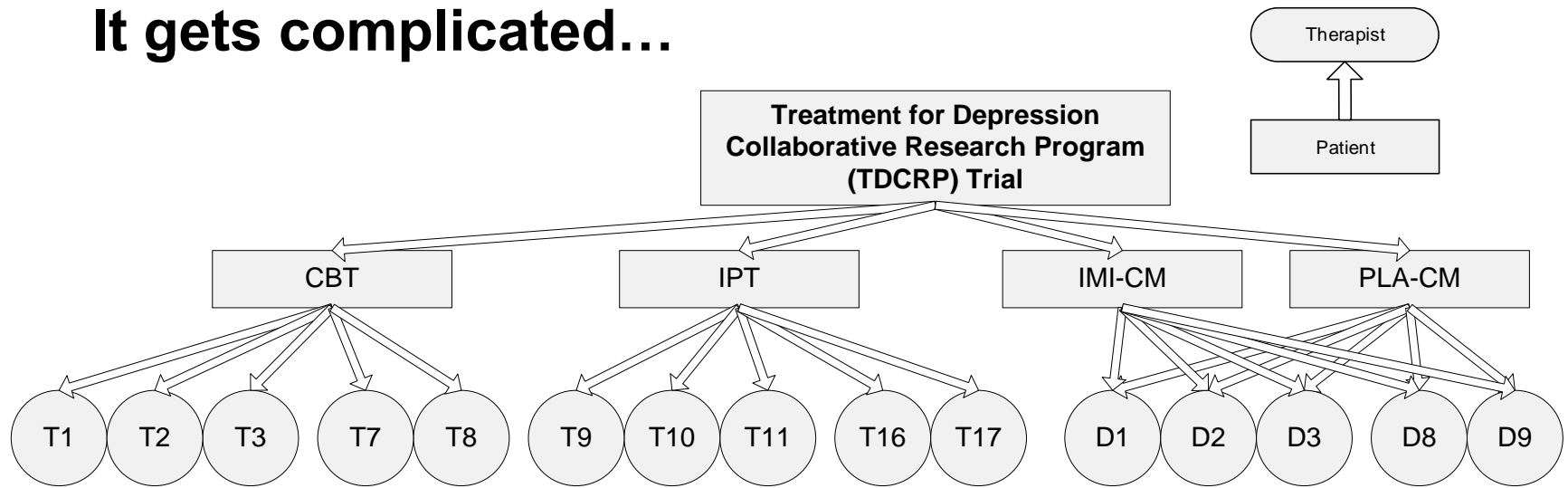


Trial Designs – Care Providers and Patients



Roberts C. Walwyn R, Design and analysis of non-pharmacological treatment trials with multiple therapists per patient. *Statistics in Medicine*, 2013, **32**, 81-98

It gets complicated...



Trial Designs – Conclusions

- There is a need to **improve reporting of the trial designs** – it is not enough to state that a trial is multicentre, individually-randomised and parallel-group (=> **standardised terminology, figure**).
- The **default** is a nested or partially nested design in psychotherapy but a crossed or partially crossed design in surgery (discussion on **pros and cons** of both options summarised in paper).
- However, **all possible design combinations** are found in psychotherapy trials so it is not safe to assume it – it needs to be **explicitly reported**.
- The **large number of design options** means that it is not helpful to regard each as a separate off-the-shelf trial design. Instead, the features (and implications) of the design should be considered and trialists should feel comfortable putting them together for their trial.
- The **intended** design may not match the **actual** design...



Implications for Precision

- **Primary Analysis Model**

- **Two-level heteroscedastic model** recommended for nested and partially nested designs (see Roberts & Roberts, 2005).
- This leads to an intra-cluster correlation coefficient **per trial arm** (*hence treatment-related clustering*).
- Where clustering is partial, the cluster-level variance is **constrained to be zero** in the arm(s) with no clustering.
- Often assumed **clustering is homogeneous across time** (combine literatures on treatment-related clustering and learning curves).
- It may be that the intervention has an **impact on the mean and on the variance** of the outcome distribution.



Implications for Precision (Nested Designs)

- Preliminary tests...
- Lee and Thompson (2005) suggested a random coefficient model

$$y_l = \alpha_l + \theta t_l + u_{therapist}^{(2)}(l) + v_{therapist}^{(2)}(l)t_l + e_l^{(1)}$$

- Roberts and Roberts (2005) suggested a two-level heteroscedastic model

$$y_l = \alpha_l + \theta t_l + u_{therapist}^{(2)}(l) + v_{therapist}^{(2)}(l)t_l + e_l^{(1)} + \xi_l^{(1)}t_l$$

- Recommended parameterisation

$$y_l = \alpha_l + \theta t_l + u_{0therapist}^{(2)}(l)(1 - t_l) + u_{1therapist}^{(2)}(l)t_l + e_{0l}^{(1)}(1 - t_l) + e_{1l}^{(1)}t_l$$



Implications for Precision (Other Designs)

- Partially nested design (constrain therapist variance in control arm to be zero – clusters of size one)

$$y_l = \alpha_l + \theta t_l + u_{1\text{therapist}}^{(2)} t_l + e_{0l}^{(1)} (1 - t_l) + e_{1l}^{(1)} t_l$$

- Crossed design (two alternatives)

$$y_l = \alpha_l + \theta t_l + u_{\text{therapist}}^{(2)} t_l + v_{\text{therapist}}^{(2)} t_l + e_l^{(1)}$$

$$y_l = \alpha_l + \theta t_l + p_{\text{therapist}}^{(3)} t_l + q_{\text{treat}}^{(2)} t_l + e_l^{(1)}$$

- Partially crossed designs...



Implications for Precision (Sample Size: Nested)

- Based on summary-level analysis of unequal variance t-test – exact method Moser *et al* (NQuery, Stata routine)
- Moser *et al* accounts for uncertainty in the cluster level variance estimates via degrees of freedom related to number of therapists

Table: Sample Size and Power for a Nested Design using Moser *et al*¹² Methods

$\rho_u = \sigma_u^2 / (\sigma_u^2 + \sigma_e^2)$	Therapists in each intervention arm	Patients per therapist	Total trial patient sample size	Power
	<i>No clustering</i>		128	80%
0	5	13	130	68%
0.025	5	13	130	56%
0.05	5	13	130	48%
	Increasing numbers of patients per therapist			
0	5	18	180	81%
0.025	5	30	300	80%
0.05	5	130	1300	80%
	Increasing numbers of therapists			
0	7	13	182	86%
0.025	8	13	208	83%
0.05	9	13	234	80%

Note: $\alpha=0.05$ (two-sided); standardised effect size is 0.5

Implications for Precision (Sample Size: Crossed)

Table. Sample Size to Achieve 80% Power in a Crossed Design with Model (2.10)

$\rho_q = (\sigma_q^2) / (\sigma_q^2 + \sigma_e^2)$	Number of Therapists	Minimum number of patients per therapist to achieve 80% power	Total trial patient sample size	Power
<i>No therapist effect</i>		-	128	80%
0	8	22	176	81%
0.025	8	30	240	81%
0.05	8	44	352	80%
0	12	14	168	84%
0.025	12	16	192	83%
0.05	12	18	216	81%
0	16	10	160	84%
0.025	16	10	160	80%
0.05	16	12	192	83%

Note: $\alpha=0.05$ (two-sided); standardised effect size is 0.5

Implications for Internal Validity

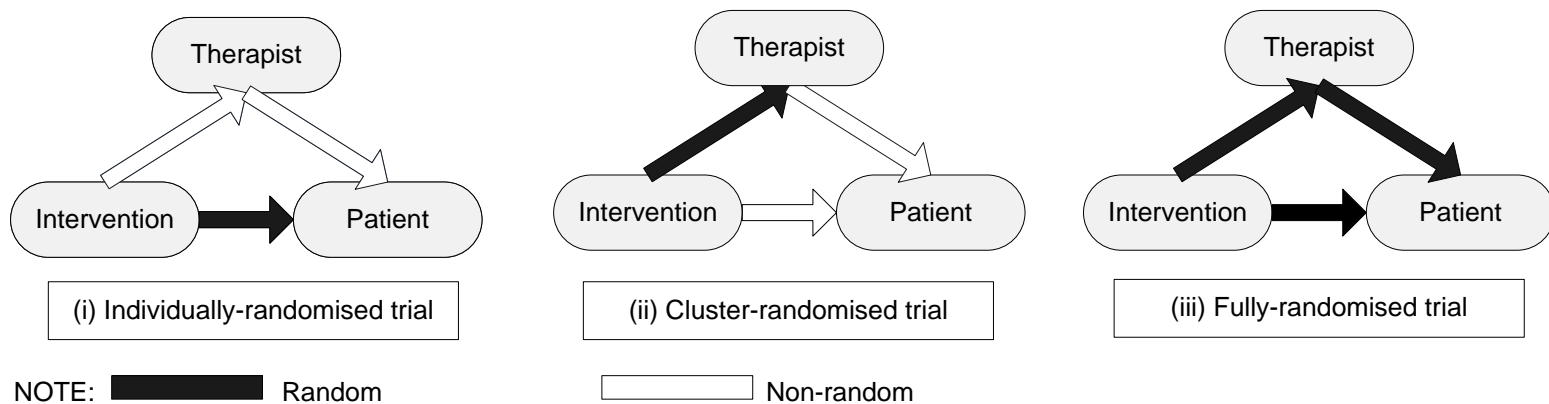
- **Selection Bias**

- The **first** relates to how *interventions are allocated to therapists* and affects the causal interpretation of intervention effects.
- The **second** relates to how *therapists are allocated to patients* and affects the causal interpretation of therapist variation.
- It is important to consider **concealing allocations** in both cases.
- The **implications of non-random or purposive allocation of interventions to therapists** will depend to some extent on the research question.
 - Problematic where interest is isolated to particular therapeutic approaches or to particular therapist characteristics.
 - Little or no concern where the intervention is intentionally a package (e.g. PACE).

Implications for Internal Validity

- Where therapist variation is of interest in its own right, random allocation of *therapists to patients* is important.
- In some circumstances it may be desirable or practical to maintain pre-existing therapist-patient allocations.
- **Practical experience** of additional randomisations; interpretation must be done with care.

Figure. Some Possible Allocation Schemes for Nested Designs



Implications for Internal Validity

Crossed Designs

- **Parallels can be drawn** between parallel-group/crossover trial designs and nested/crossed designs at the level of the therapist.
 - Interventions are allocated to patients within the former but to therapists within the latter.
- **In a crossed design, patients within therapists correspond to periods within patients** in a crossover trial.
 - The point in the sequence at which a patient is assigned to the therapist is equivalent to the *period* in a crossover trial.
 - If each **therapist were to treat just two patients**, intervention sequences might be allocated to therapists as they are to patients in an AB/BA crossover design.
 - **As therapists typically treat more than two patients**, intervention sequences would generally be longer so that these designs are more likely to be comparable to replicate crossover trials.



Implications for External Validity

- **Basis for Generalisation**
- **Fixed versus random effects**
 - Martindale (1978): **Random selection** of patients and therapists is necessary for intervention effects to be generalised to their respective populations and therapists must be included as a **random-effect** in analyses for generalisations to be made on a statistical basis.
 - Siemer and Joorman (2003) argue in favour of **fixed-effects** approach.
- **Selection of therapists (Elkin, 1999)**
 - Formal eligibility criteria (one or more populations).
- **Baseline therapist characteristics (Elkin, 1999)**
 - By arm and therapist sample
 - Therapists equally representative of “clinical practice” by arm
- **Flow of therapists through trial (Elkin, 1999)**
 - CONSORT diagram for patients AND therapists

Conclusions

- Psychotherapy trials are characterised not only by the complexity of their interventions but also of their designs and data structures.
- Greater consideration should be given to broad principles of experimental design. Trialists should justify what is appropriate and feasible to address their particular research question, appreciating the consequences of adopting a set design and analysis strategy.
- Clearer and more precise reporting of research questions, trial designs and therapist variation is therefore needed, as is prospective gathering of therapist data.
- Even if multiple randomisations are not feasible or appropriate, considering them aids the understanding of potential biases associated with observational aspects of a therapist design.

Ongoing and Planned Further Research

- Therapist variation in meta-analyses and meta-regressions
 - Systematic review of Cochrane reviews
 - Methods for absolute mean differences
 - Methods for standardised mean differences
 - Methods for intra-cluster correlation coefficients (ICCs)
 - Illustration using trials of counselling in primary care
- Practical illustration of more complex designs and analyses
 - Illustrative examples (e.g. PACE), also reporting ICCs
 - Experience of additional randomisations
 - Group-based intervention trials
- Implications for early-phase trial designs
 - Assessment of potential efficacy
 - Empirical optimisation of complex interventions (build on DoE)
- Crossed designs
 - Formal experimental designs for estimating learning curves

