Design and analysis of randomised trials with treatment-related clustering

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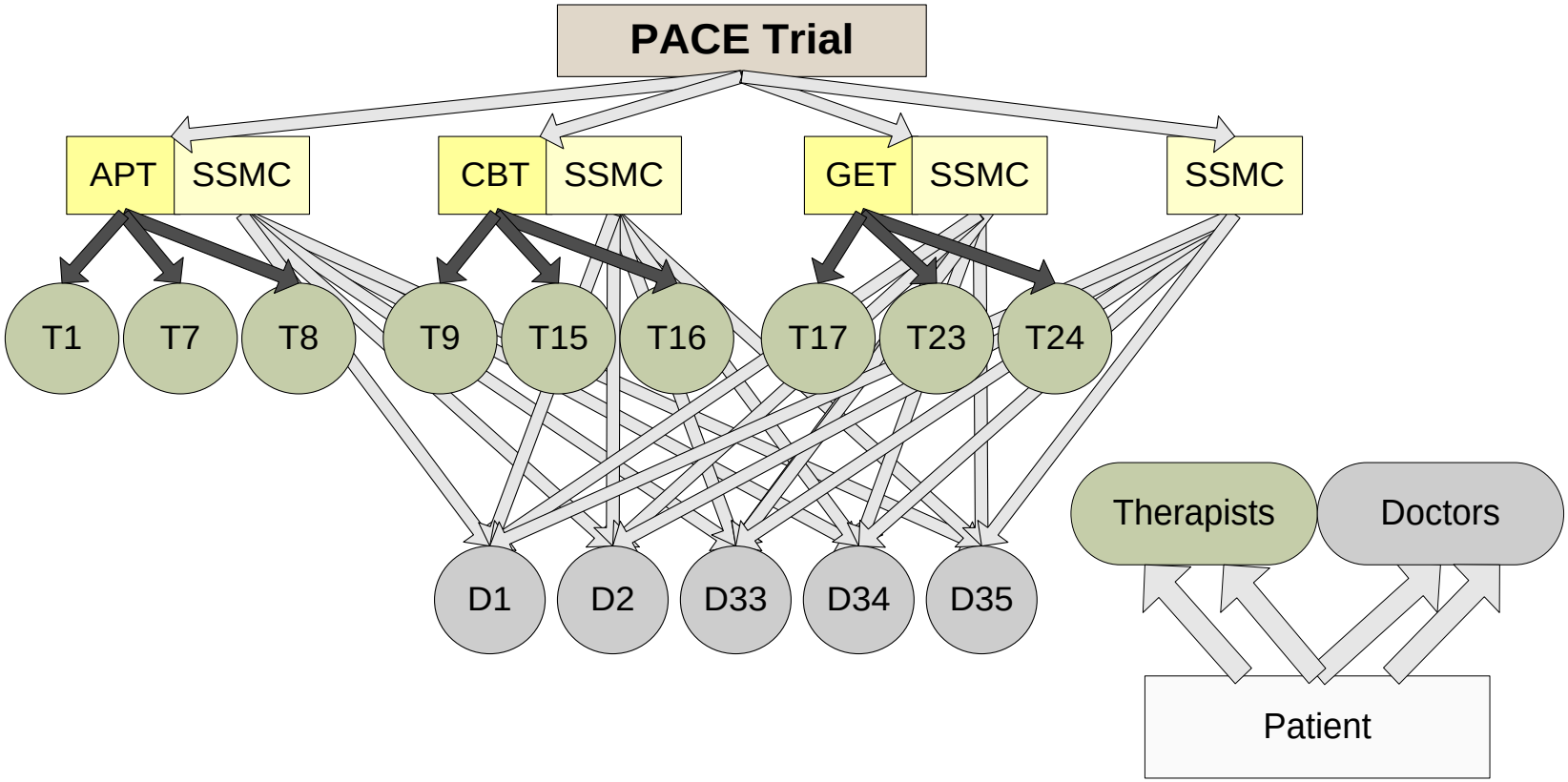
- Walwyn R, Roberts C. Therapist variation in randomised trials of psychotherapy: Implications for precision, internal and external validity. *Statistical Methods for Medical Research*, 2010, ***19***, 291-315
- Roberts C, Walwyn R. Design and analysis of non-pharmacological treatment trials with multiple 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

Example:		**Techniques**	
		Counselling	Advice
Therapists	Counsellors	A	B
	GPs	C	D

1. Techniques
2. Therapist characteristics
3. Packages

} "Complex" Interventions

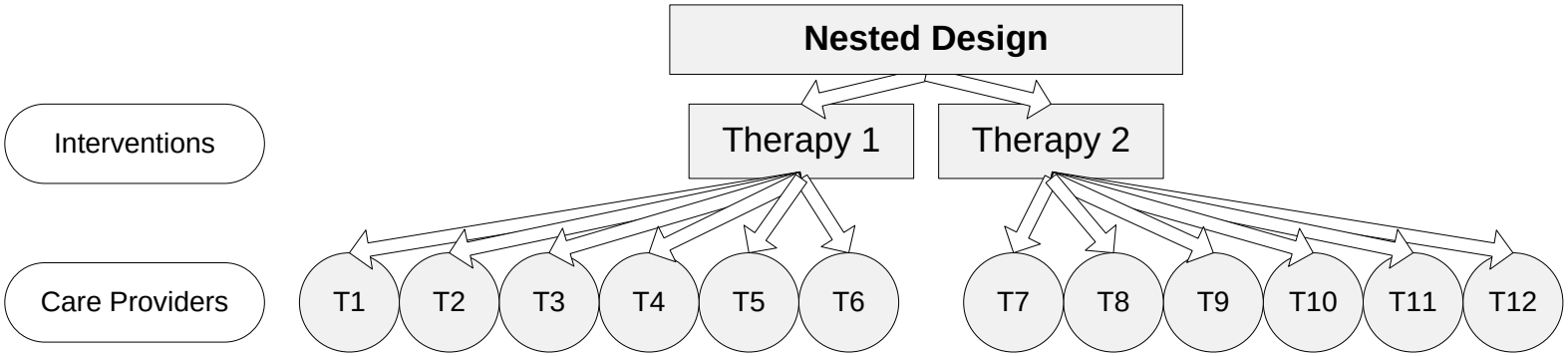
Trial Designs

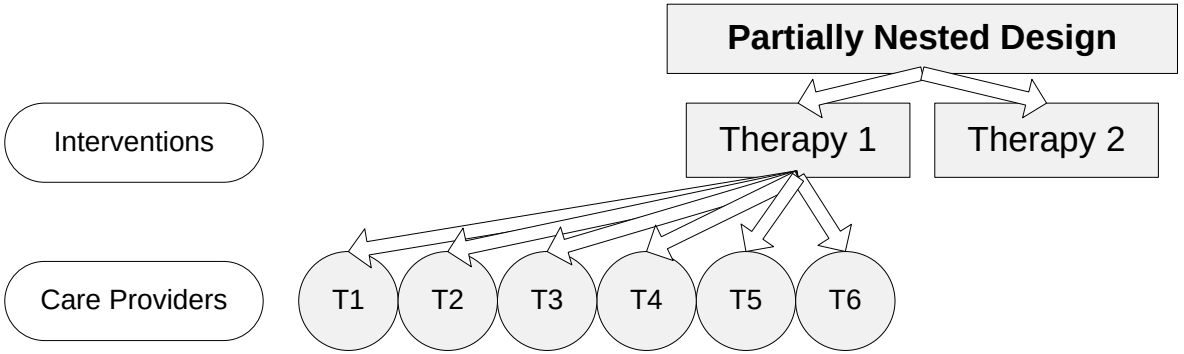
- Due to “therapists” being distinct from “behaviours”, in addition to the relationship between behaviours and patients, there are a further two relationships that need to be considered and reported:
  - Relationship between behaviours and therapists
  - Relationship between therapists and patients

- These relationships describe the data structure, which should inform the sample size calculation and method of analysis.

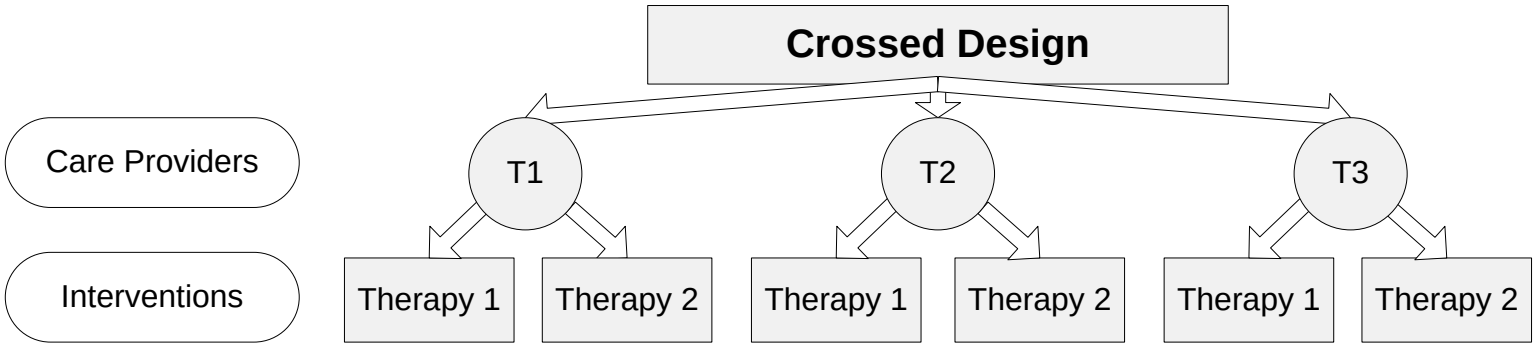
- In psychotherapy, behaviours are synonymous with treatments.
  - In my view, behaviours and therapists are two components of a complex intervention, each being represented by a separate “treatment variable” (plus the interaction between them). However, there is a need to standardise the terminology used.

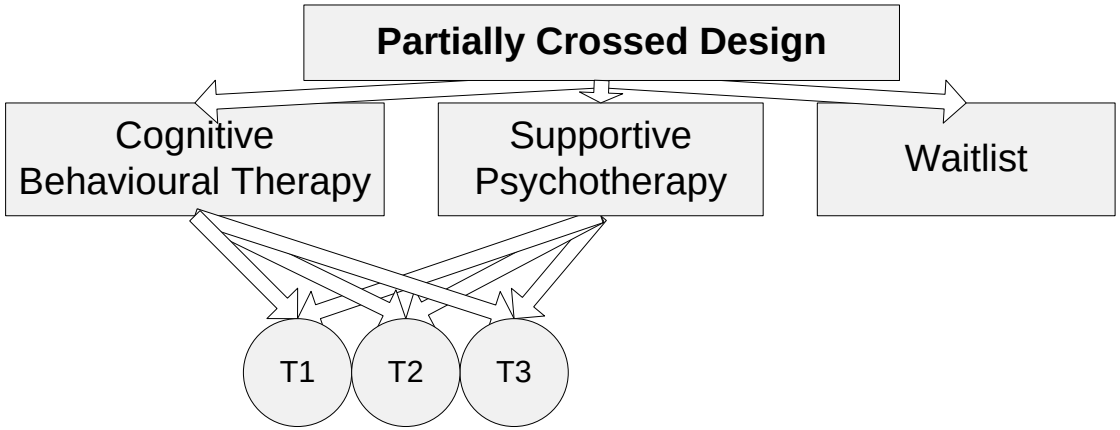
Trial Designs – Interventions and Care Providers (1)



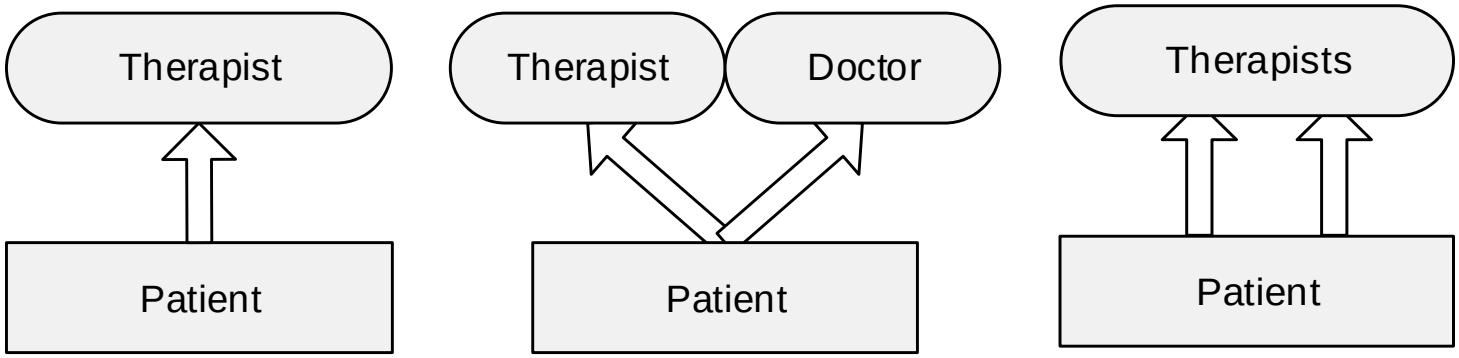


Trial Designs – Interventions and Care Providers (2)



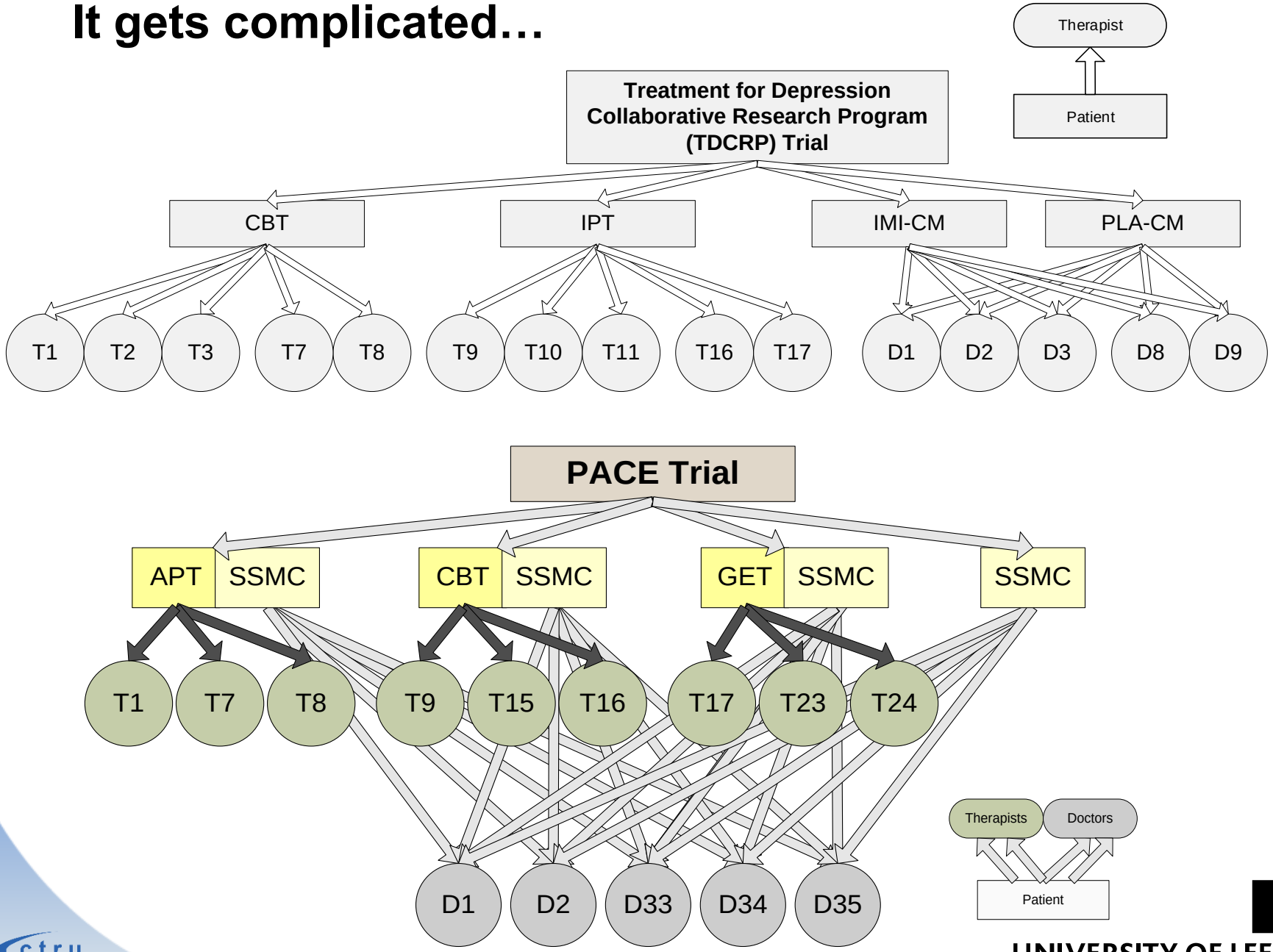


Trial Designs – Care Providers and Patients



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

$$y_l = \alpha_l + \theta t_l + u^{(2)}_{therapist\ (l)} + v^{(2)}_{therapist\ (l)} t_l + e^{(1)}_l$$

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

$$y_l = \alpha_l + \theta t_l + u^{(2)}_{therapist\ (l)} + v^{(2)}_{therapist\ (l)} t_l + e^{(1)}_l + \xi^{(1)}_l t_l$$

- Recommended parameterisation

$$y_l = \alpha_l + \theta t_l + u^{(2)}_{0\,therapist\ (l)} (1 - t_l) + u^{(2)}_{1\,therapist\ (l)} t_l + e^{(1)}_{0l} (1 - t_l) + e^{(1)}_{1l} t_l$$

Implications for Precision (Other Designs)

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

$$y_l = \alpha_l + \theta t_l + u^{(2)}_{1\,therapist\ (l)} t_l + e^{(1)}_{0l}\left(1 - t_l\right) + e^{(1)}_{1l} t_l$$

- Crossed design (two alternatives)

$$y_l = \alpha_l + \theta t_l + u^{(2)}_{therapist\ (l)} + v^{(2)}_{therapist\ (l)} t_l + e^{(1)}_l$$

$$y_l = \alpha_l + \theta t_l + p^{(3)}_{therapist\ (l)} + q^{(2)}_{treat\ (l)} + e^{(1)}_l$$

- 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*[112] 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***
	No clustering		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: α=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
No therapist effect		-	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: α=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.

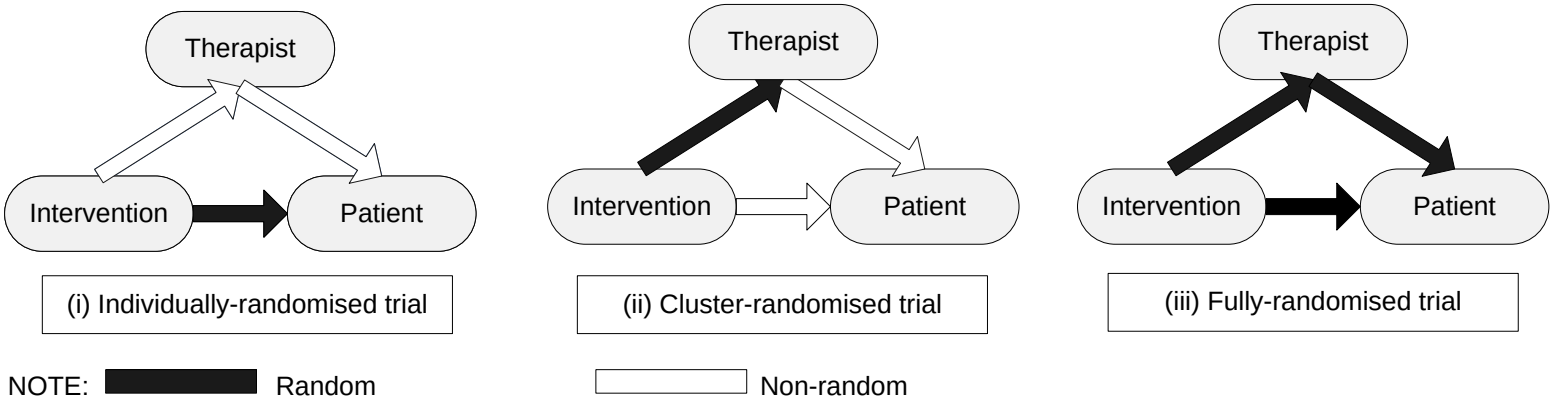
- The implications of non-random or purposive allocation of *interventions to therapists* will depend to some extent on the research question.
  - Problematic where interest is isolated to particular therapeutic approaches or to particular therapist characteristics.
  - Little or no concern where the 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