Non-Orthogonal Factorial Designs for Trials of Therapist-Delivered Interventions: Allowing for Therapist Capacity, Availability and Turnover

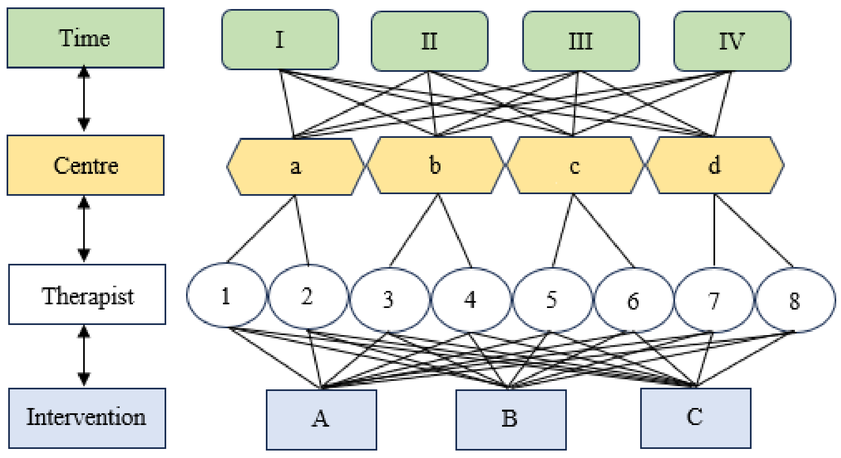
Arpan Singh[1], Steven G Gilmour[2] and Rebecca EA Walwyn[1]

[1]Leeds Institute for Clinical Trials Research, University of Leeds
[2]Department of Mathematics, King's College London

1. Overview

Motivating Example

- Suppose that we are planning a trial of a new psychotherapy (intervention) which is to be compared to a control therapy such as CBT.
- The therapies are individually delivered by therapists that are nested within trial centres.
- Therapists deliver both the interventions to different patients (Crossed Therapist-Intervention design).
- Objective – estimate the fixed intervention effect.



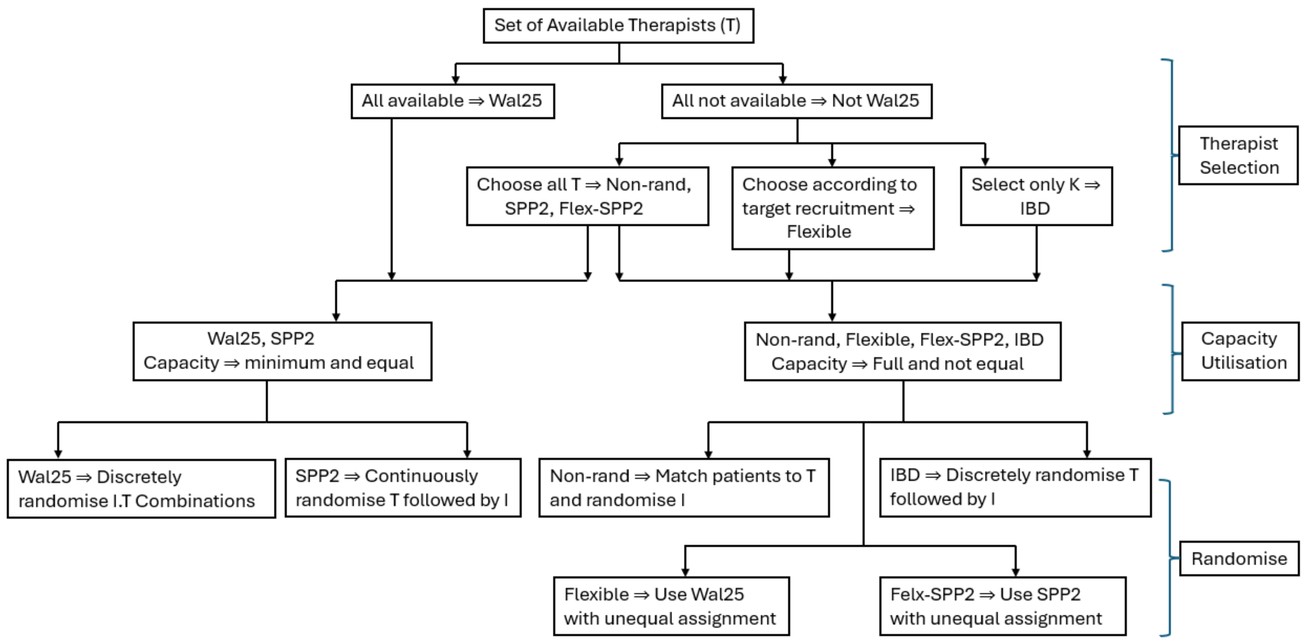
Practical Constraints

- **Capacity:** maximum number of patients a therapist can treat in a time window (batch).
- **Availability:** Therapist's readiness to accept new patients at the point of patient randomisation.
- **Turnover:** Changes in the therapist pool over time.
- **Question:** How to efficiently design the trial taking these practical constraints into account? What are the impacts?

2. Randomisation Methods

Existing Methods

1. **Non-rand :** Non-random assignment of patients to therapists
2. **Wal25:** Walwyn et al. 2025 – Randomise patients to I.T combinations orthogonally
3. **SPP2:** Shapiro et al. 1990 – Two step randomisation of patients to I followed by to T



Novel Methods

1. **IBD:** Incomplete block design for Therapists – Dynamically sample the therapists from the pool of available therapists at a time point
2. **Flexible:** Flexible version of Wal25 – Randomise patients to I.T combinations non-orthogonally
3. **Flex-SPP2:** Flexible version of SPP2 – Two step randomisation of patients to I followed by to T (accounting for capacity)

3. Analysis Models

M-1 Linear Crossed Random Effects Model

$$y_{ijkl} = \delta_0 + \delta_1 I_{ijkl} + u_{1j} + u_{2k} + u_{3jk} + u_{4l} + u_{5kl} + v_{1j} I_{ijkl} + v_{2k} I_{ijkl} + v_{3jk} I_{ijkl} + v_{4l} I_{ijkl} + v_{5kl} I_{ijkl} + e_{ijkl}$$

(i,j,k,l) : (P, T, B, C)
(δ_0, δ_1) : (overall mean, intervention effect)
I_{ijkl} : +1/-1 coding for intervention 1/2
$(u_{1j}, u_{2k}, u_{3jk}, u_{4l}, u_{5kl})$: (T, B, TB, C, BC) random effects
$(v_{1j}, v_{2k}, v_{3jk}, v_{4l}, v_{5kl})$: (IT, IB, ITB, IC, IBC) random effects

M-2 Learning Effects Model

$$y_{ijl} = \delta_0 + \delta_1 I_{ijl} + \delta_2 t_{ijl} + \delta_3 t_{ijl} I_{ijl} + w_{1j} + w_{2j} t_{ijl} + w_{3l} + w_{4l} t_{ijl} + z_{1j} I_{ijl} + z_{2j} t_{ijl} I_{ijl} + z_{3l} I_{ijl} + z_{4l} t_{ijl} I_{ijl} + e_{ijl}$$

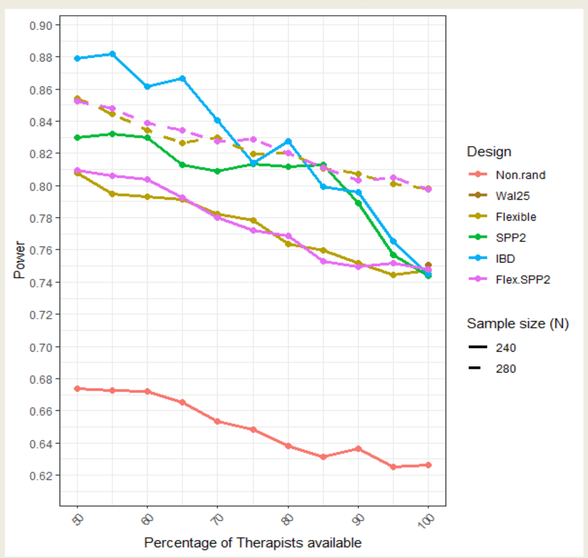
(δ_2, δ_3) : (time in therapist, time in therapist in the intervention)
t_{ijl} : # patients treated prior to patient i by therapist j in centre l
$(w_{1j}, w_{2j}, w_{3l}, w_{4l})$: (T, T-learning, C, C-learning)
$(z_{1j}, z_{2j}, z_{3l}, z_{4l})$: (IT, IT-learning, IC, IC-learning)

Simulations

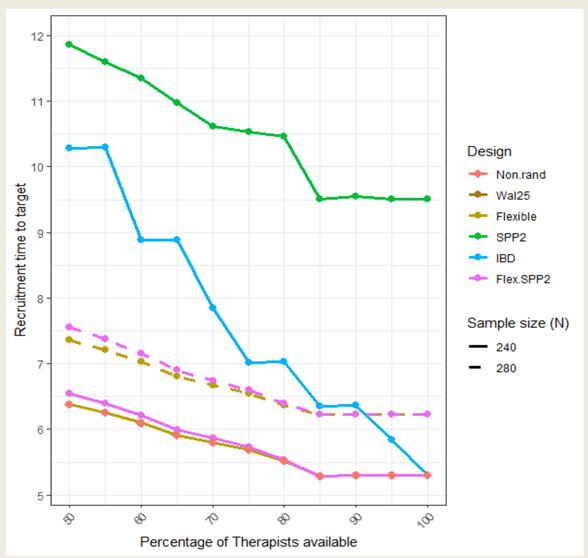
- Simulate the data from combinations of
  - Designs given in section 2
  - Various hypothetical single and multi-centre trials based on #(P, T, B, C)
  - A range of availabilities (a) and capacities (a_E) of the therapists
- Fit the same model from which the data was originally generated.

4. Results

Model M-1: Power vs Availability



Model M-1: Recruitment time to target vs Availability



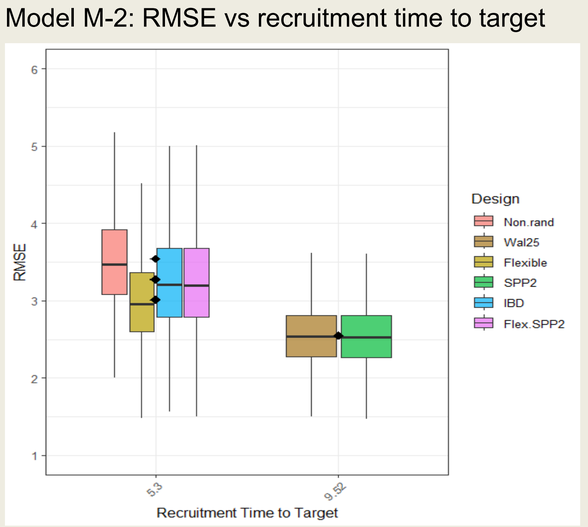
Model M-1

	Design	δ_1	SE(δ_1)	$\sigma^2_{u_1}$	$\sigma^2_{v_1}$	T-2 error	Boundary	Fail	RMSE
True values		0.4	-	0.1	0.15	-	-	-	-
(n_B ,a_E, a)	Non-rand	0.4	0.144	1.10	0.15	0.36	0.74	0.01	1.68
=	Wal25	0.398	0.129	0.11	0.14	0.33	0.44	0.91	0.97
= (5, 0.5, 1)	Flexible	0.398	0.127	0.11	0.14	0.24	0.39	0.01	0.96
	SPP2	0.398	0.13	0.1	0.15	0.2	0.4	0.9	0.96
	IBD	0.401	0.128	0.11	0.15	0.24	0.38	0.01	0.96
	Flexible-SPP2	0.399	0.127	0.11	0.14	0.24	0.38	0.01	0.96

Model M-2

	Design	δ_1	SE(δ_1)	$\sigma^2_{w_1}$	σ^2_{z1}	T-2 error	Boundary	Fail	RMSE
True values		0.4	-	0.1	0.15	-	-	-	-
(n_B ,a_E, a)	Non-rand	0.402	0.116	1.08	0.16	0.14	0.23	0.05	3.56
=	Wal25	0.399	0.085	0.1	0.14	0.01	0.27	0.03	2.55
= (5, 0.5, 1)	Flexible	0.397	0.087	0.11	0.14	0.02	0.29	0.03	3.02
	SPP2	0.402	0.085	0.11	0.14	0.01	0.28	0.03	2.55
	IBD	0.4	0.088	0.11	0.14	0.02	0.3	0.03	3.29
	Flexible-SPP2	0.4	0.088	0.11	0.14	0.02	0.29	0.03	3.3

Model M-2: RMSE vs recruitment time to target



5. Conclusions

- **Non-random** – Avoid
- **Existing designs** –
  1. Rigid and not cost effective
  2. Best statistical properties, provided no replication issues due to capacity
- **Proposed designs** –
  1. More pragmatic, save time and money
  2. Statistically equivalent to existing designs with a slight increase in the sample size

Contact

a.singh8@leeds.ac.uk
github.com/arpan52

This study/project is funded by the NIHR [NIHR301709]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Funded by NIHR | National Institute for Health and Care Research