Optimising the allocation of participants in a two-stage randomised experiment to estimate selection, preference and treatment effects

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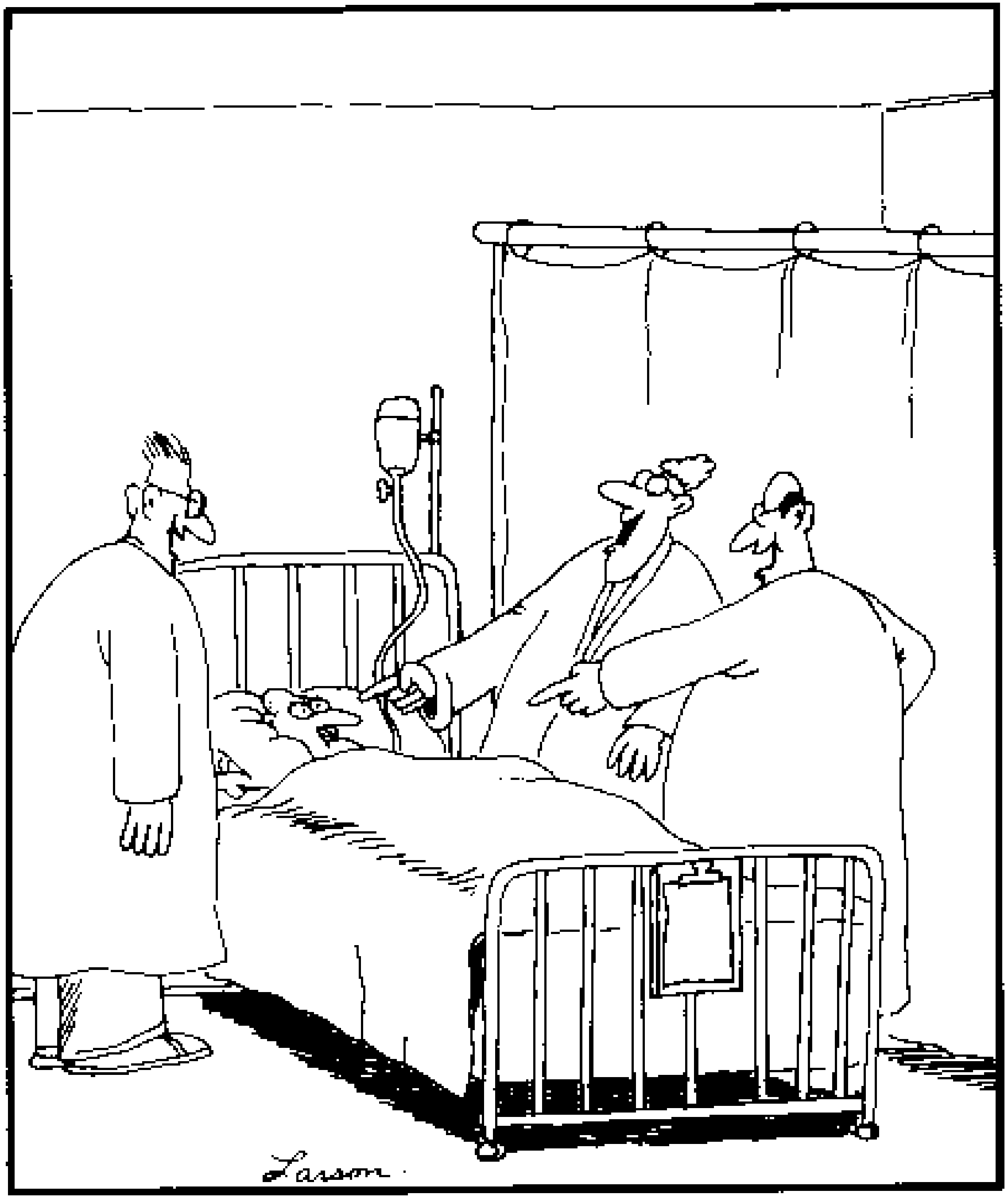


Testing whether laughter *is* the best medicine

Introduction

Treatment effect (TE): Unbiased estimate from conventional trial (all patients randomised); represents the direct effect of treatment.

Selection effect (SE): Outcome may be affected by preferences that patients have between the alternative interventions.

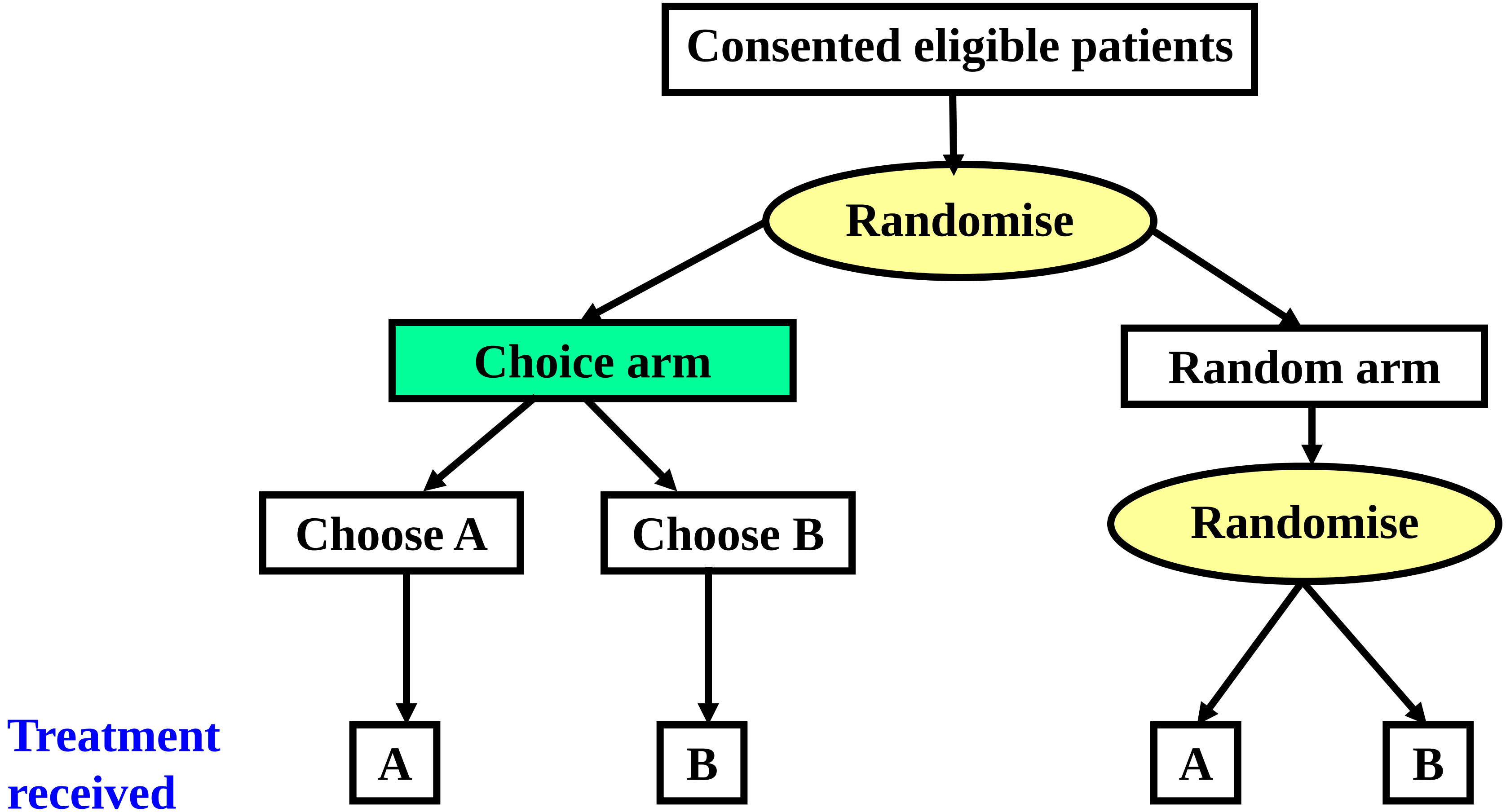
Preference effect (PE): Outcome may be affected by whether patients are actually randomised to (and hence receive) their preferred treatment. Equivalent to interaction between selected and actual treatments.

Selection and Preference effects

- SE and PE can be important, even if TE is small. E.g., patients may comply better or have a better response with a treatment they prefer.

- SE and PE cannot be estimated in the conventional randomised trial but can be estimated in a two-stage randomised design.

Two-stage randomised design



(cf. Rucker, *Stat Med*)

Two-stage design: example

- **IMAP Study (Improved Management of Mildly Abnormal Pap smears**
  - **Women with abnormal Pap smear results**
  - **Randomised to:**
    - **HPV testing**
    - **Repeat Pap test (usual care)**
    - **Informed choice group, with decision aids**
  - **Outcomes: SF36 quality of life scales**
    Satisfaction measures

Two-stage design: example

Interventions

A (Pap management): **follow-up abnormal test results with repeat Pap tests at 6 – 12 month intervals, with referral to colposcopy if more serious abnormalities are then discovered**

B (HPV management): **immediate test for the presence of Human Papilloma Virus (HPV) types that are strongly associated with the risk of cervical cancer; referral to colposcopy if positive**

Two-stage design: example

Actual treatment		Choice arm		Random arm
		Chose HPV	Chose Pap	
HPV	Sample size	50	—	76
	Mean	47.57		46.16
	SD	10.62		9.74
Pap	Sample size	—	22	64
	Mean		50.59	45.51
	SD		4.89	9.97

Objective

- Determine the optimal proportion (θ) of patients to be allocated to the choice arm, to estimate TE, SE, PE.
  - Optimum will depend on whether investigators are interested primarily in SE and PE, or jointly in all of TE, SE and PE.

Model

$$Y_{ijk} = \mu + \tau_i + \nu_j + \pi_{ij} + \varepsilon_{ijk}$$

for patient *k*, receiving actual treatment *i*, and would select treatment *j*

Constraints

$$\sum_i \tau_i = 0$$

$$\alpha \nu_1 + \beta \nu_2 = 0$$

$$\alpha \pi_{i1} + \beta \pi_{i2} = 0, \text{ for } i = 1, 2$$

where *α* and *β* are the proportions of participants in the choice arm who choose treatments A and B respectively

IMAP, observed and estimated means: SF 36 Mental Component Score

	Informed Choice		**Random**		
Actual Treatment	Preferred HPV	Preferred Pap	Preferred HPV	Preferred Pap	Total (random)
Received HPV	47.57	*N/A*			46.16
Received Pap	*N/A*	50.59			45.51
Proportion preferring	α=0.694	β=0.306	TE =	46.16–45.51	= 0.65

[shaded box] = observed values

IMAP, observed and estimated means: SF 36 Mental Component Score

	Informed Choice		Random		
Actual Treatment	Preferred HPV	Preferred Pap	Preferred HPV	Preferred Pap	Total (random)
Received HPV	47.57	*N/A*	47.57		46.16
Received Pap	*N/A*	50.59		50.59	45.51
Proportion preferring	α=0.694	β=0.306	TE =	46.16–45.51	= 0.65

(cyan) =	observed values
(yellow) =	values for random arm inferred from the informed choice arm

IMAP, observed and estimated means: SF 36 Mental Component Score

	Informed Choice		**Random**		
Actual Treatment	Preferred HPV	Preferred Pap	Preferred HPV	Preferred Pap	Total (random)
Received HPV	47.57	*N/A*	47.57	42.96	46.16
Received Pap	*N/A*	50.59	43.28	50.59	45.51
Proportion preferring	α=0.694	β=0.306	TE =	46.16–45.51	= 0.65

(blue)	=	observed values
(yellow)	=	values for random arm inferred from the informed choice arm
(orange)	=	estimated

Effects of interest

Treatment effect: $\boldsymbol{TE = \tau_1 - \tau_2}$

- Unbiased estimate from the random arm: $\mu_1 - \mu_2$
- Same estimate as traditional RCT, but less precise

Effects of interest

Selection effect: $\boldsymbol{SE} = \Delta v = v_1 - v_2$

In terms of model parameters:

$$\Delta\nu = \frac{1}{2}\left[(\mu_{11} + \mu_{21}) - (\mu_{12} + \mu_{22})\right]$$

In terms of observable means:

$$\hat{\Delta\nu} = \frac{1}{2\hat{\alpha}\hat{\beta}m}(z_1 - z_2)$$

where $z_1 = m_1(\bar{X}_1 - \bar{Y}_1)$ $\quad z_2 = m_2(\bar{X}_2 - \bar{Y}_2)$

α (β) are the proportions who prefer treatment A (B)

$\bar{X}_1, \bar{X}_2$ are mean responses for choice arm, $\bar{Y}_1, \bar{Y}_2$ for random arm

$\mathrm{m}_1(\mathrm{m}_2) =$ number choosing A(B); $\mathrm{m} =$ total in choice arm

Effects of interest

Preference effect: $\boldsymbol{PE = \pi_{11} - \pi_{12} - \pi_{21} + \pi_{22}}$

In terms of model parameters:

$$\Delta\pi = \frac{1}{2}\left[\mu_{11} - \mu_{12} - \mu_{21} + \mu_{22}\right]$$

In terms of observable means:

$$\hat{\Delta}\pi = \frac{1}{2\hat{\alpha}\hat{\beta}m}\left(z_1 + z_2\right)$$

where $z_1 = m_1\left(\overline{X}_1 - \overline{Y}_1\right)$ $z_2 = m_2\left(\overline{X}_2 - \overline{Y}_2\right)$

α (β) are the proportions who prefer treatment A (B)

$\overline{X}_1$, $\overline{X}_2$ are mean responses for choice arm, $\overline{Y}_1, \overline{Y}_2$ for random arm

$\mathrm{m}_1(\mathrm{m}_2)$ = number choosing A(B); m = total in choice arm

Treatment, preference and selection effects: SF 36 Mental Component Score

1. **Treatment Effect** $TE = \Delta\tau =$ **0.65 (HPV – Pap)**

2. **Selection Effect** $SE = \Delta\nu =$ **–1.35 (HPV – Pap)**

3. **Preference Effect** $PE = \Delta\pi =$ **5.96**

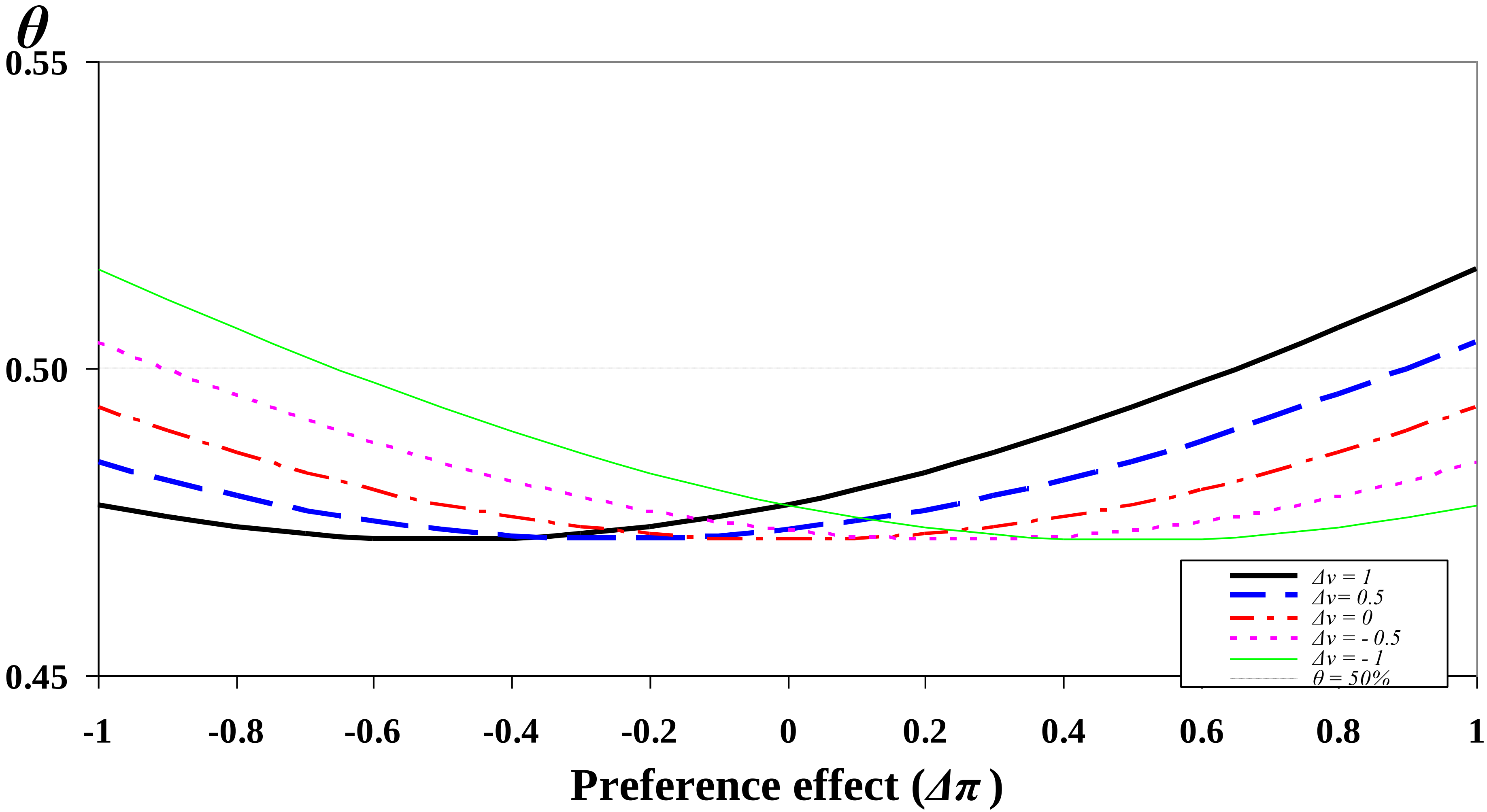
$\text{var}(\Delta\hat{\nu})$ as function of $\Delta\nu$ and $\Delta\pi$…

$$\text{var}(\Delta\hat{\nu}) = \frac{1}{4\alpha^2(1-\alpha)^2 N\theta}\left[\alpha\sigma_{11}^2 + (1-\alpha)\sigma_{22}^2 + \alpha(1-\alpha)[(2\alpha-1)\Delta\nu + \Delta\pi]^2 + 2\left(\frac{\theta}{1-\theta}\right)\left(\alpha^2\sigma_1^2 + (1-\alpha)^2\sigma_2^2\right)\right]$$

Optimal θ satisfies

$$\left(\frac{\theta}{1-\theta}\right)^2 = \frac{\alpha\sigma_{11}^2 + (1-\alpha)\sigma_{22}^2 + \alpha(1-\alpha)[(2\alpha-1)\Delta\nu + \Delta\pi]^2}{2\left[\alpha^2\sigma_1^2 + (1-\alpha)^2\sigma_2^2\right]}$$

Optimal proportion (θ) in choice group for estimation of selection effect (Δν), α = 0.75, variances constant



Difference in optimal θ with SE or PE criteria

$$\theta_\nu - \theta_\pi = \left(\Delta\pi^2 - \Delta\nu^2\right)/\,32$$

Difference is small in most practical cases.

Example: $\Delta\pi = 1$ and $\Delta\nu = 0$

$$\theta_\nu - \theta_\pi = 1/32 = 3.1\%$$

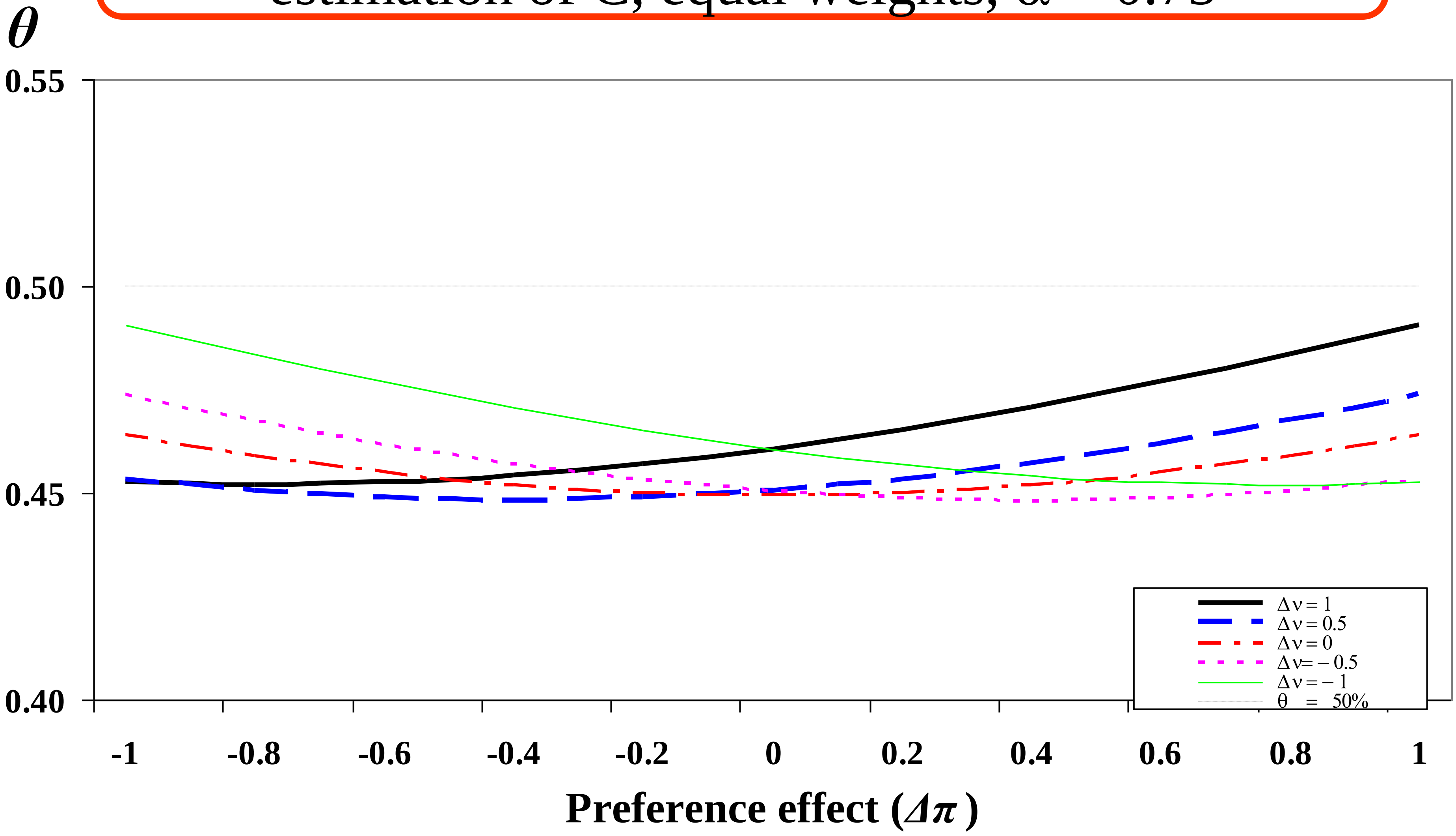
Optimisation when TE, SE and PE are all of interest

Minimise the linear function:

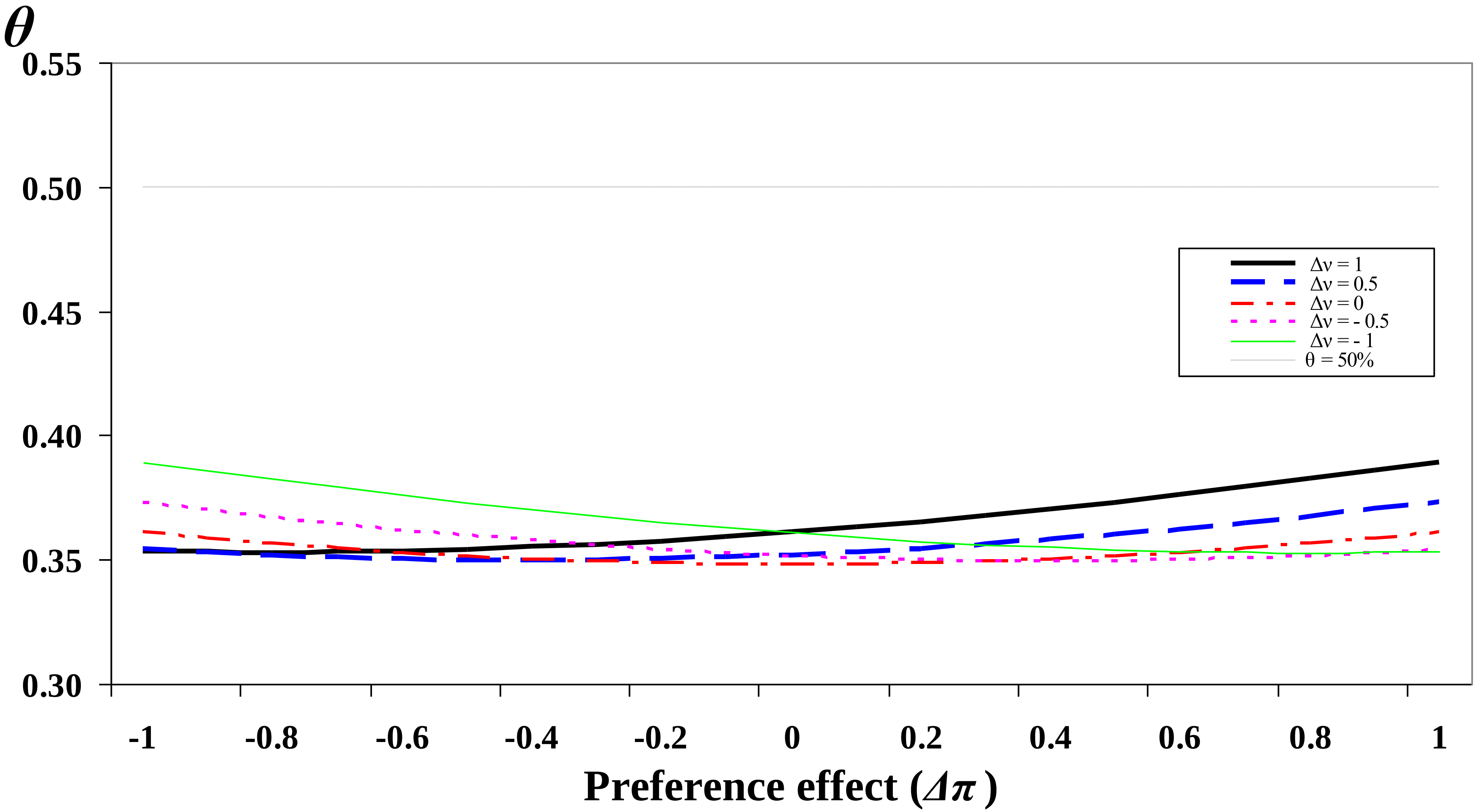
$$C = w_{\tau}\ \mathrm{var}\left(\Delta\hat{\tau}\right) + w_{\tau}\ \mathrm{var}\left(\Delta\hat{\nu}\right) + w_{\pi}\ \mathrm{var}\left(\Delta\hat{\pi}\right)$$

where w's represent relative interest in TE, SE and PE

Optimal proportion (θ) in choice group for estimation of C, equal weights, α = 0.75



Optimal proportion (θ) in choice group to estimate C, $w_\tau = 0.8$, $w_\nu = 0.1$, $w_\pi = 0.1$, $\alpha = 0.75$



Discussion

Have determined the optimal allocation of participants to the choice arm of a two-stage design.

- depends on relative interest in TE, SE or PE.
- optima for SE and PE are different (but close!)
- optimum is between ⅓ and ½ for many scenarios

Discussion

- Implications if SE and/or PE dominate TE?
- Does being asked to choose a treatment affect the outcome, as opposed to simply experiencing ones chosen treatment (or not)?
- See McCaffrey, Walter et al., *Medical Decision Making 2011* and associated editorial.
- Technical details in *Stat Med* (Walter et al., *provisionally accepted*).

Further research topics

- Compare overall outcomes in the choice arm to overall outcomes in the random arm.
  - This contrasts measure the effect of being <u>offered</u> a choice of treatment, and involve SE and PE.
- Generalise to allow for some participants being undecided or indifferent to their choice of treatment.
- Power and sample size for this design.


Thanks!