Do you want your surgeon to be an expert?

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SSO, Ottawa – January 2008

Or…Design and analysis of clinical experiments taking patient / clinician preferences and expertise into account

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Outline

- Review of experimental designs that recognise clinician and patient preferences
- Introduction to the expertise-based (EB) trial design
- Development of EB analysis
  - EB *vs*. conventional design
  - Efficiency vs. effect size
- Example
- Discussion points

The randomisation paradigm….

(Treatment A) (Statistician) (Treatment B)

The randomisation paradigm….

…but this can often go wrong in practice.

- Patients change their minds
- Doctors change their minds
- Crossover to the other treatment
- Drop-out from either study treatment
- Failure to comply with therapy

PREFERENCES

Alternative trial designs taking clinician and patient preferences into account:

Features include:

- <u>who</u> is randomised (or not)
- <u>when</u> they are randomised
- <u>how</u> they are randomised

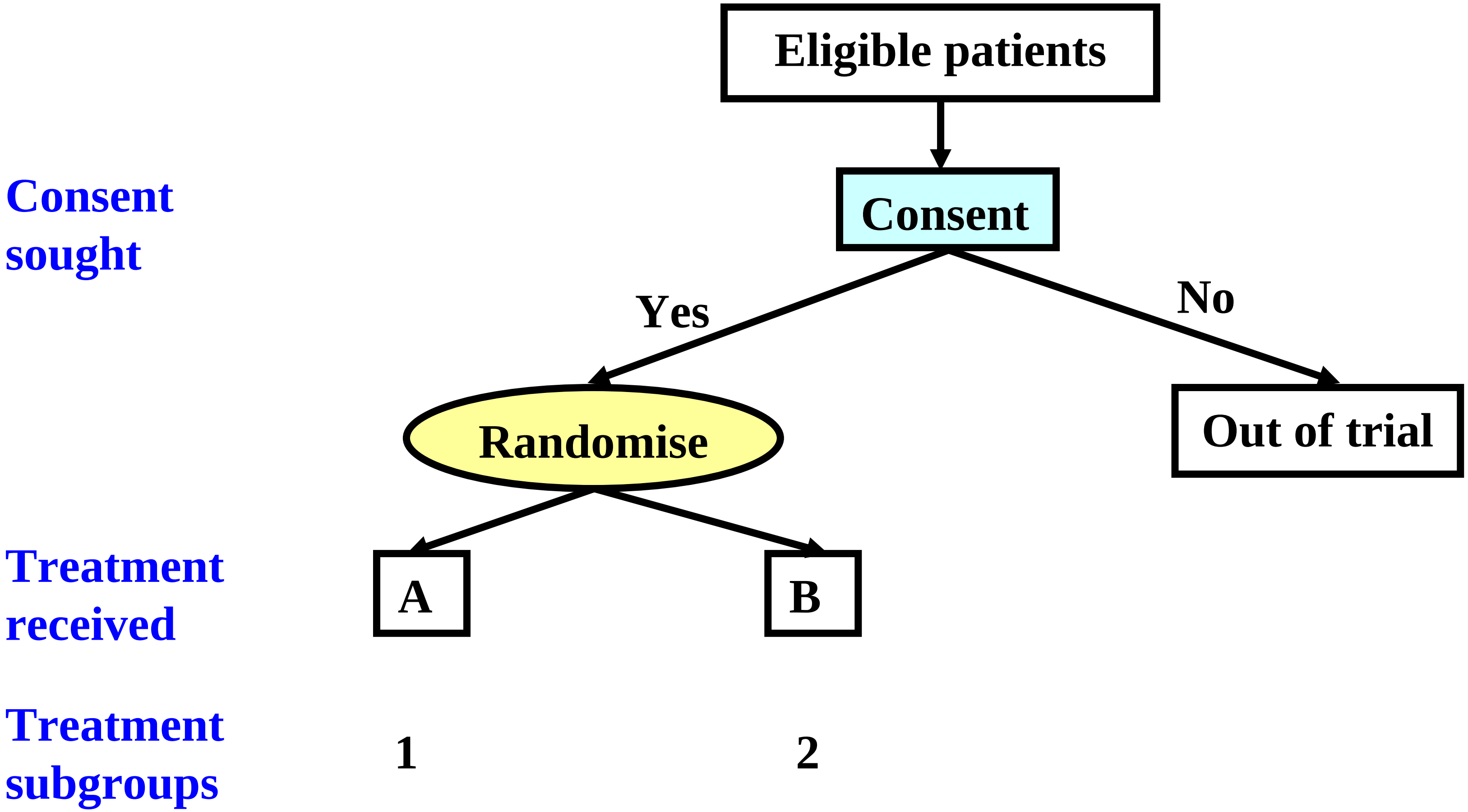
Recognition of :

- <u>Patient</u> preferences
- <u>Clinician</u> preferences (often based on expertise)
- <u>Both</u> (e.g. decision aid designs)

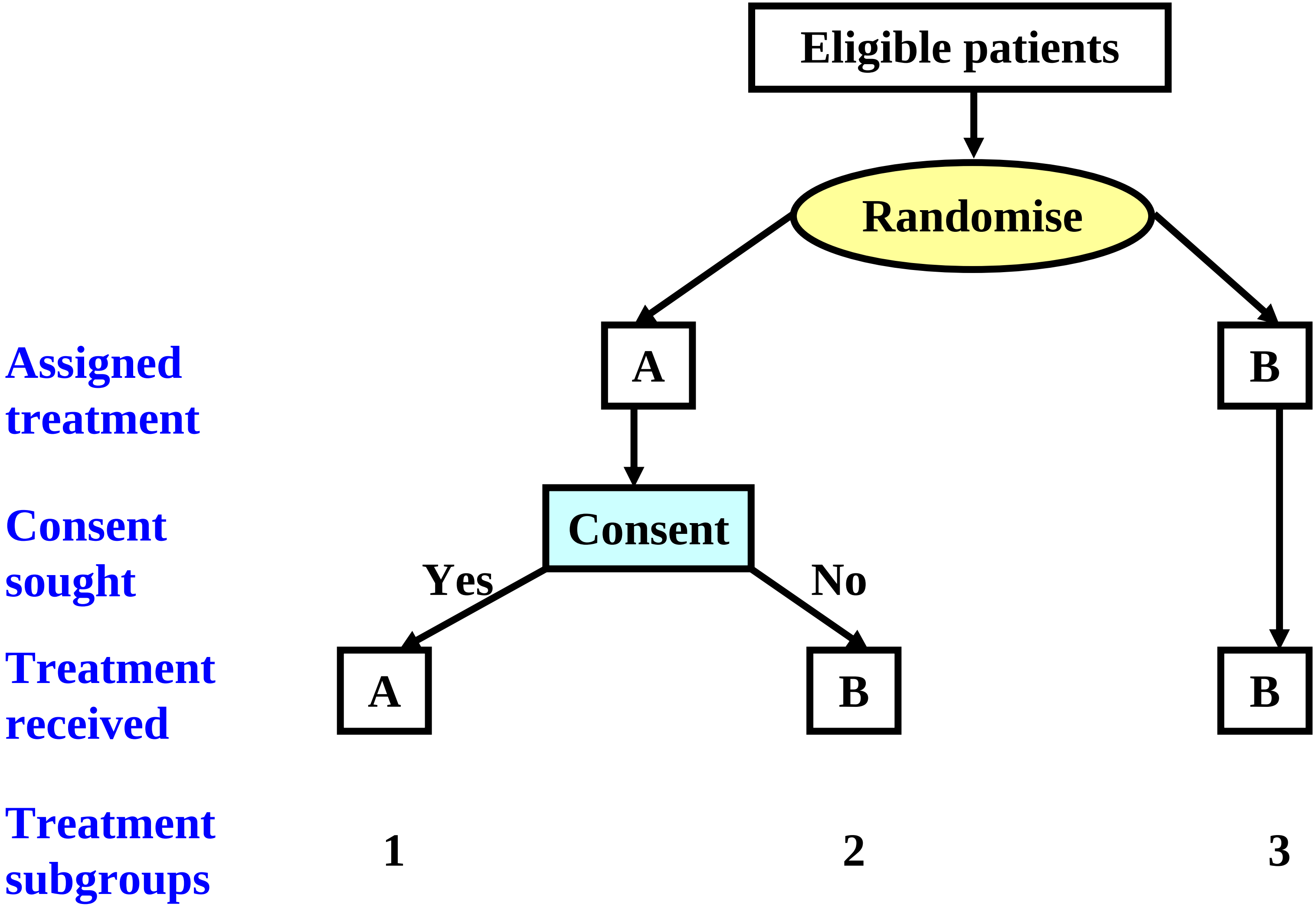
Alternative trial designs

1. Conventional RCT
2. Zelen’s single consent design
3. Partially randomised, preference design
4. Two stage randomisation design
5. Decision aid studies
6. Preference-based <u>analysis</u> of conventional design
7. Expertise-based design

1. Conventional RCT



2. Zelen's single consent design

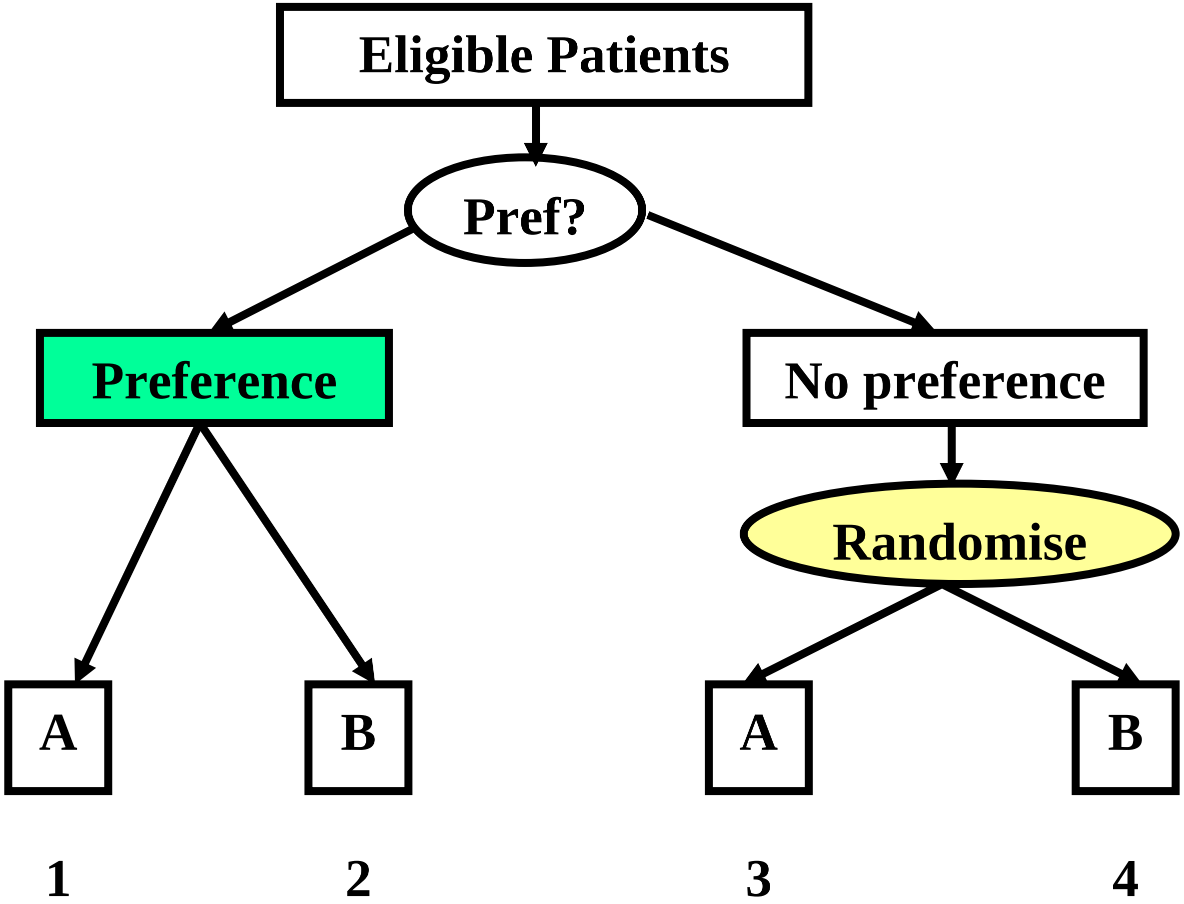


3. Partially randomised, preference design

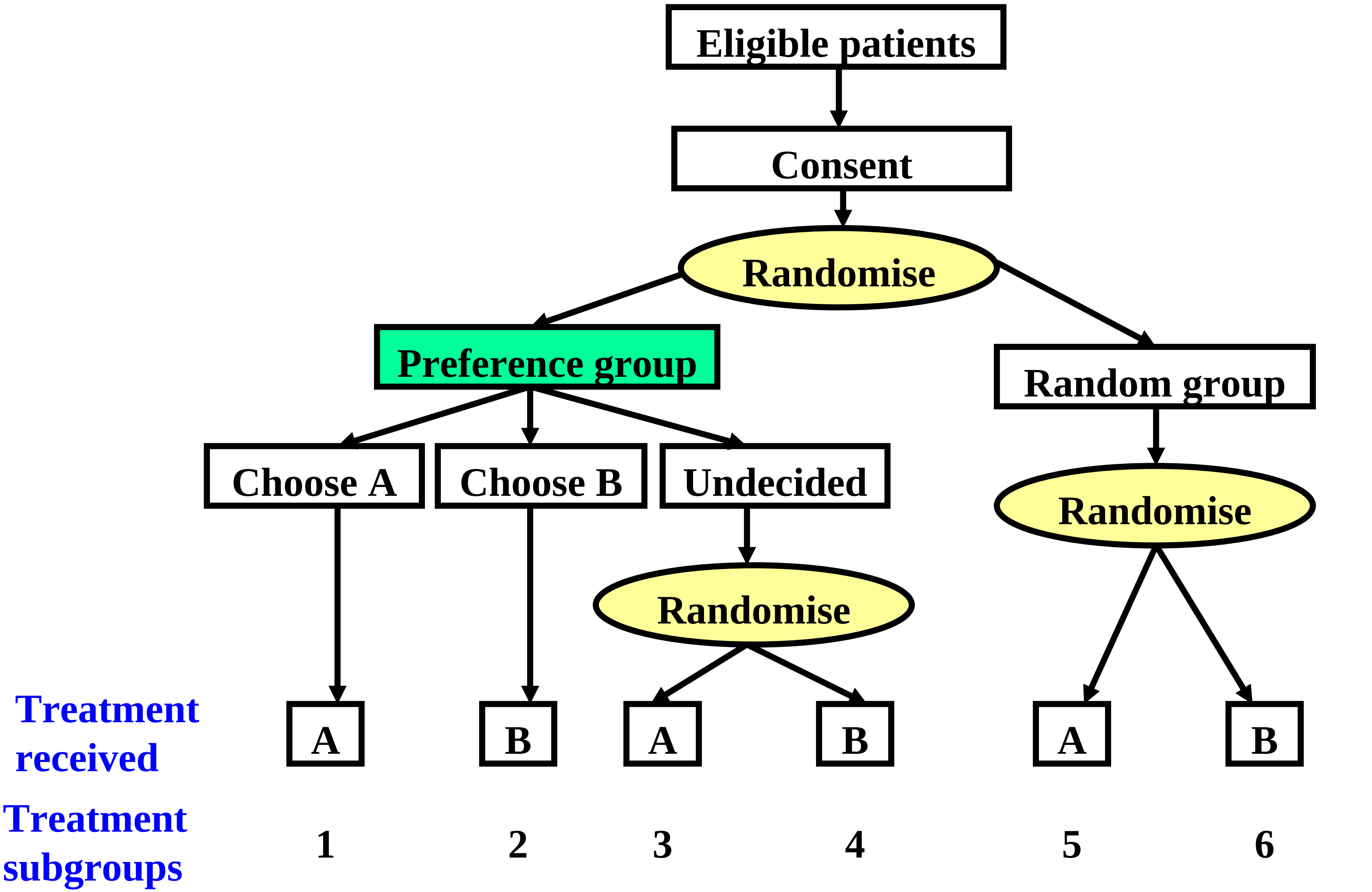
Preference ascertained

Treatment received

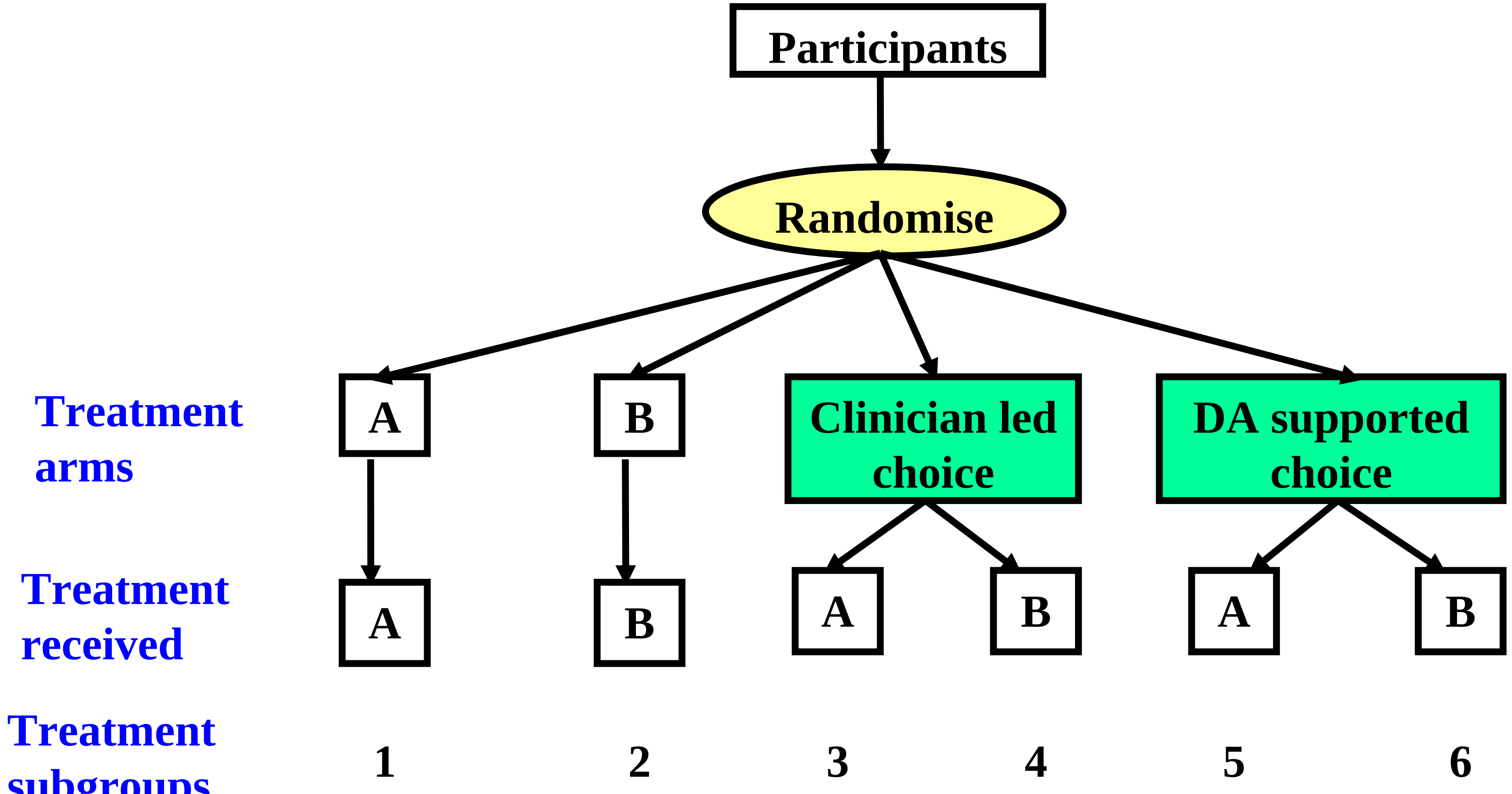
Treatment subgroups



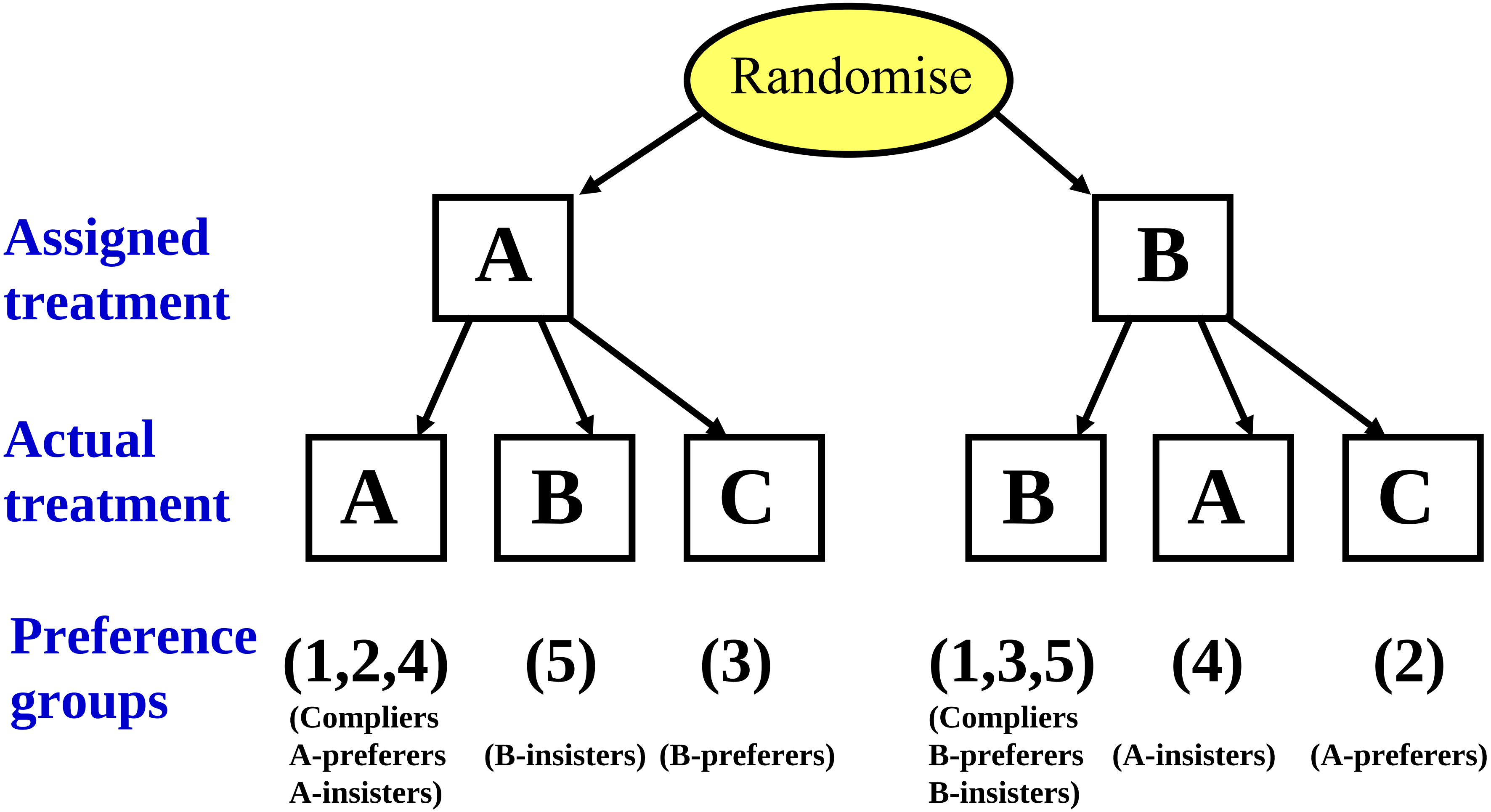
4. Two-stage randomisation design



5. Decision aid studies



6. Preference-based analysis of conventional RCT



6… Framework for preference-based analysis

Group	Actual Treatment if offered A	Actual Treatment if offered B	Description
1	A	B	Compliers
2	A	C	A-preferers
3	C	B	B-preferers
4	A	A	A-insisters
5	B	B	B-insisters

C = neither A nor B

Preference can result from patient or clinical decisions

Analytic goal: estimate treatment effect by preference

Journal of Clinical Epidemiology
ELSEVIER
Journal of Clinical Epidemiology 59 (2006) 685–696

ORIGINAL ARTICLES

A new preference-based analysis for randomized trials can estimate treatment acceptability and effect in compliant patients

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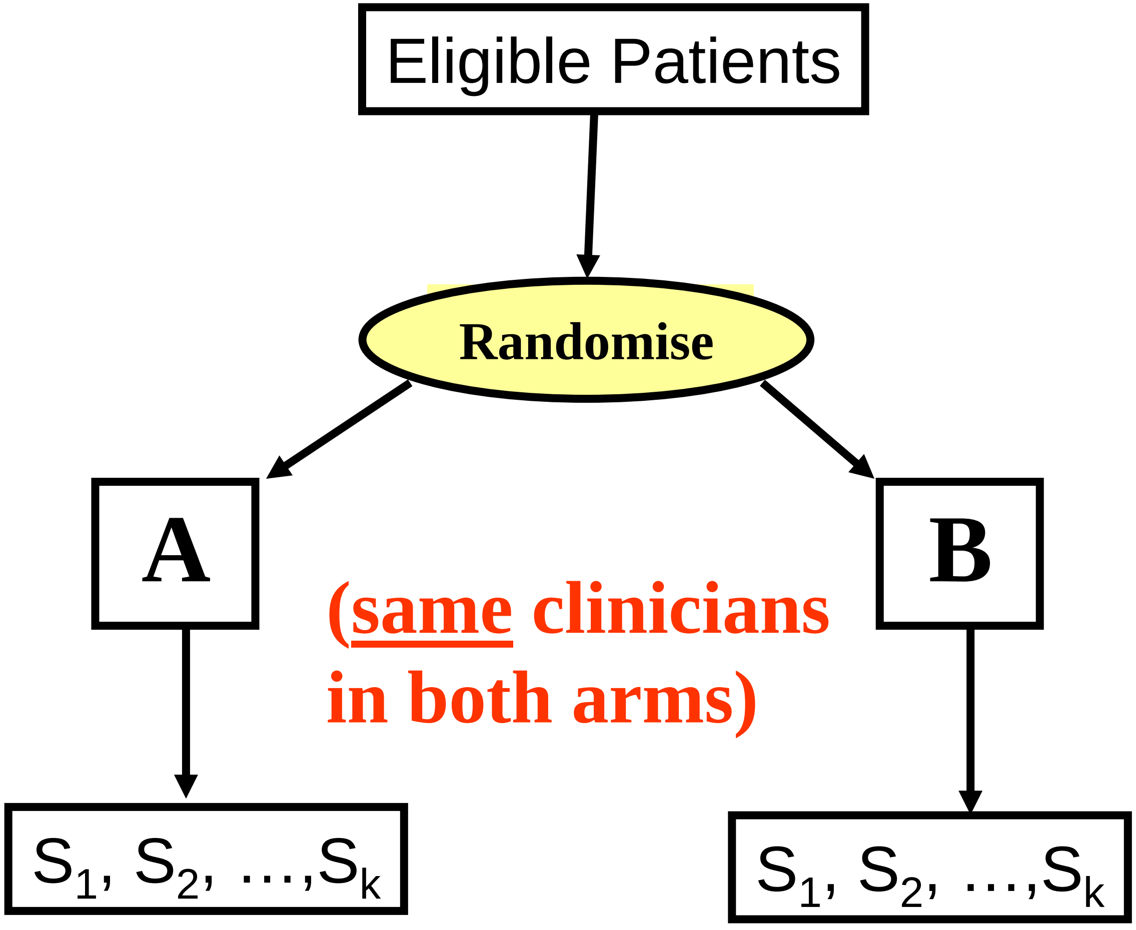
Walter et al., J Clin Epid 59, 685-96, 2006

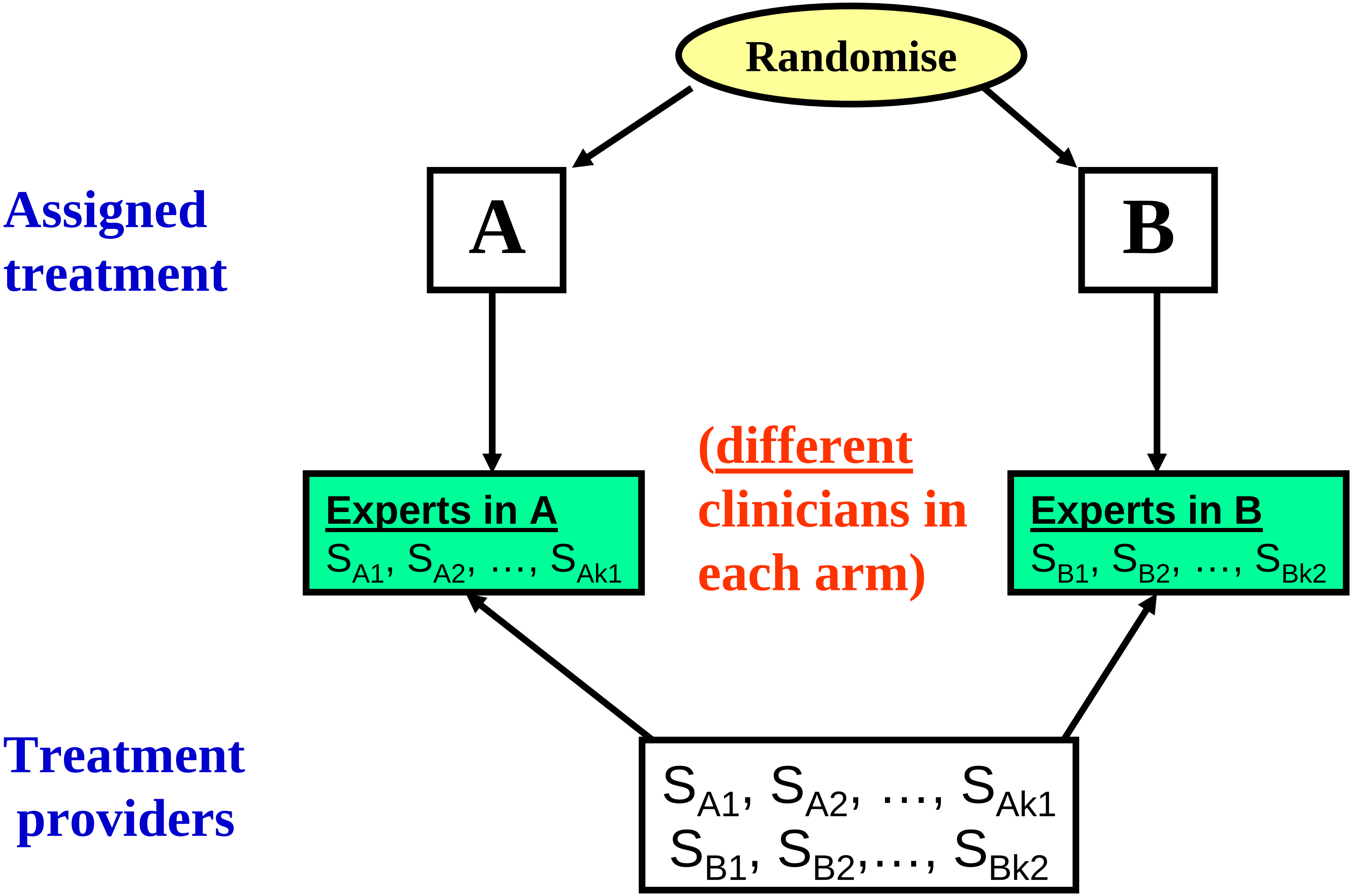
7. Expertise effect in conventional design



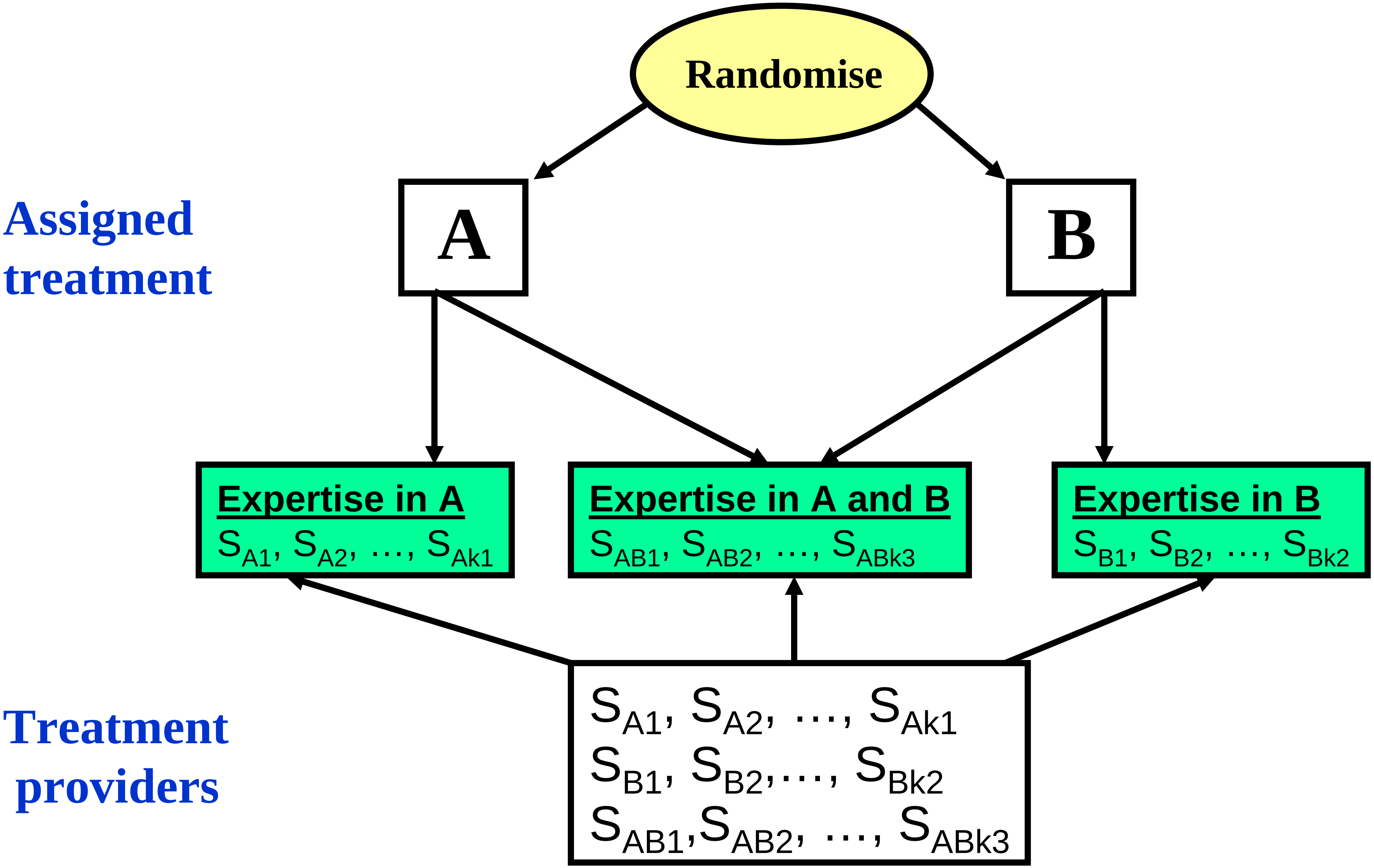
Assigned treatment

Treatment providers

7…Expertise-based design



7…Expertise-based (hybrid) design



Need for expertise based randomised controlled trials

P J Devereaux, Mohit Bhandari, Mike Clarke, Victor M Montori, Deborah J Cook, Salim Yusuf, David L Sackett, Claudio S Cinà, S D Walter, Brian Haynes, Holger J Schünemann, Geoffrey R Norman and Gordon H Guyatt

BMJ 2005;330;88-

Devereaux et al, BMJ <u>330</u>, 88-, 2005

Advantages of EB design

- Recognition of clinician preferences
  - Clinical preferences always exist
    - Not all techniques are covered equally in medical training (some not at all!)
    - Doctors usually believe one treatment is better
    - True equipoise is rare
  - Reduces procedural crossovers
    - Avoids attenuation of treatment effect
    - This can be important even if crossover rate is low
  - Reduces co-interventions

Advantages of EB design…

- Treatment given by experts may lead to better outcomes
  - Treatment effect <u>may</u> be larger than from conventional RCT

Advantages of EB design…

- Improved ethics
  - Patients are guaranteed an expert to treat them
    - This is not possible in conventional design
    - Improves recruitment and compliance
  - Doctors deliver only their therapy of choice
    - They are not required to use their second choice on 50% of their patients
    - Improves recruitment of physicians and clinical centres

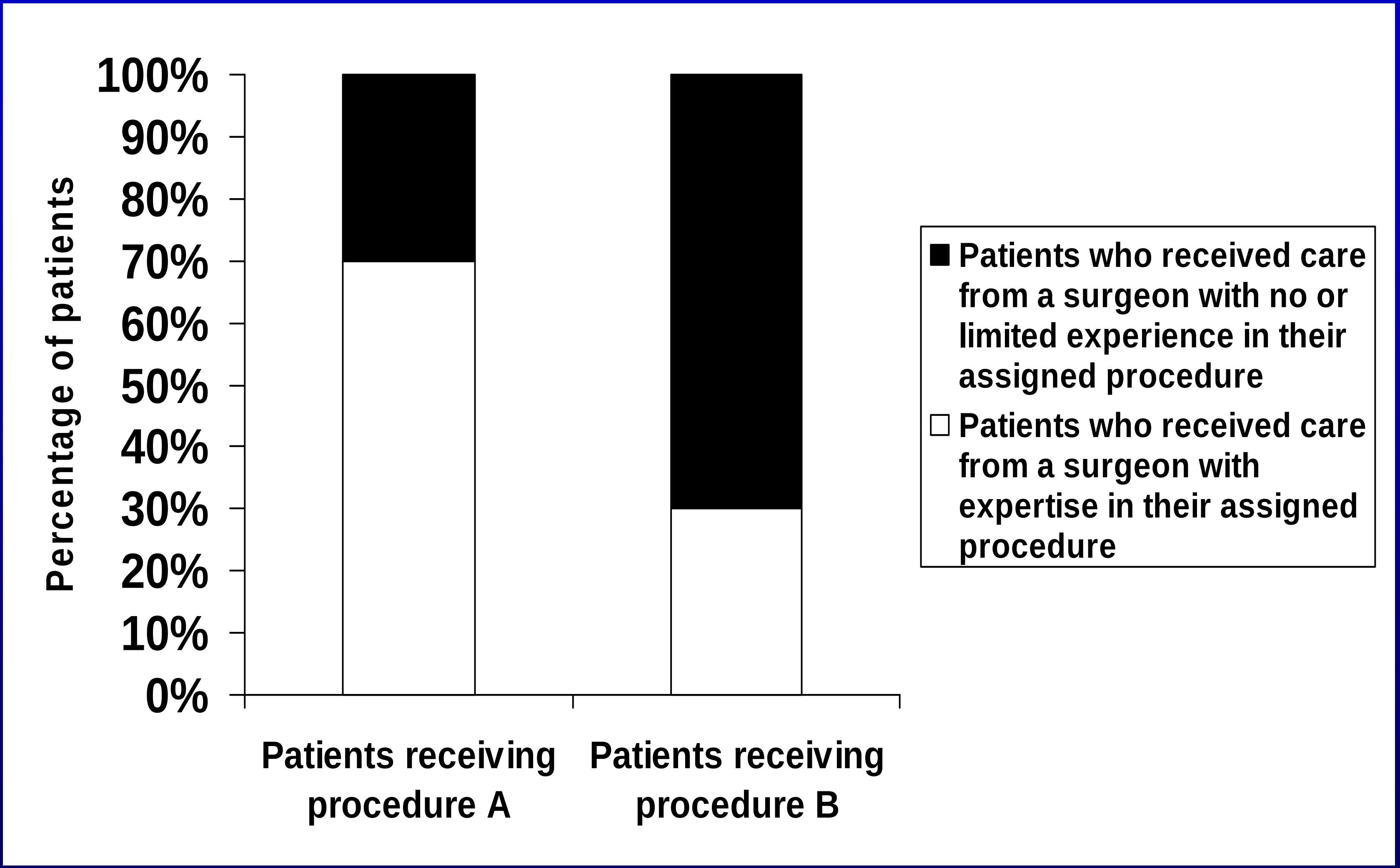
Advantages of EB design…

- Avoids “differential expertise bias”…
  - Different distribution of skill with A vs. B
  - One technique may be more common, especially if one is experimental

Expertise bias in conventional RCTs

- Clinicians individually tend to favour A or B
- If the number of cases performed by surgeons of various expertise levels is disproportionate, the less familiar technique is disadvantaged

Expertise bias in a conventional RCT



Expertise bias in a conventional RCT

- Lack of experience with new technique is sometimes countered with a "run-in" period
  - Require a minimum number of patients before admission to the trial
- This is not always successful…!

Requiring a run-in period may not solve the problem…

Example:

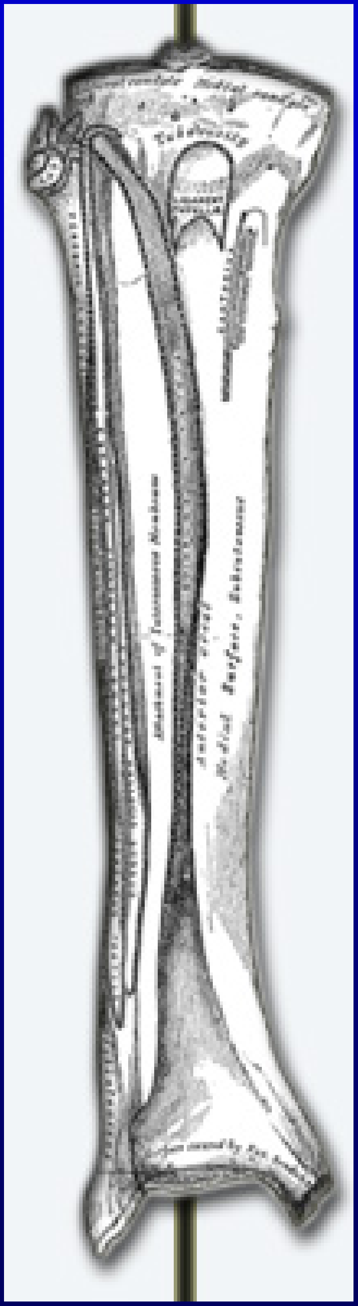
> 250 laparoscopic inguinal hernia surgeries before hernia recurrence rates significantly decreased

(Neumayer, NEJM 2004)

So clinicians may still be on a learning curve during the trial…

Example – the SPRINT study

- ✓ We will use the experience of a large multi-centre RCT to consider expertise effects, and potential advantages of using the EB design
- ✓ Conventional design was used in SPRINT, but expertise was measured



Study to Prospectively evaluate Reamed Intramedullary Nails in Tibial fractures: (S.P.R.I.N.T.)

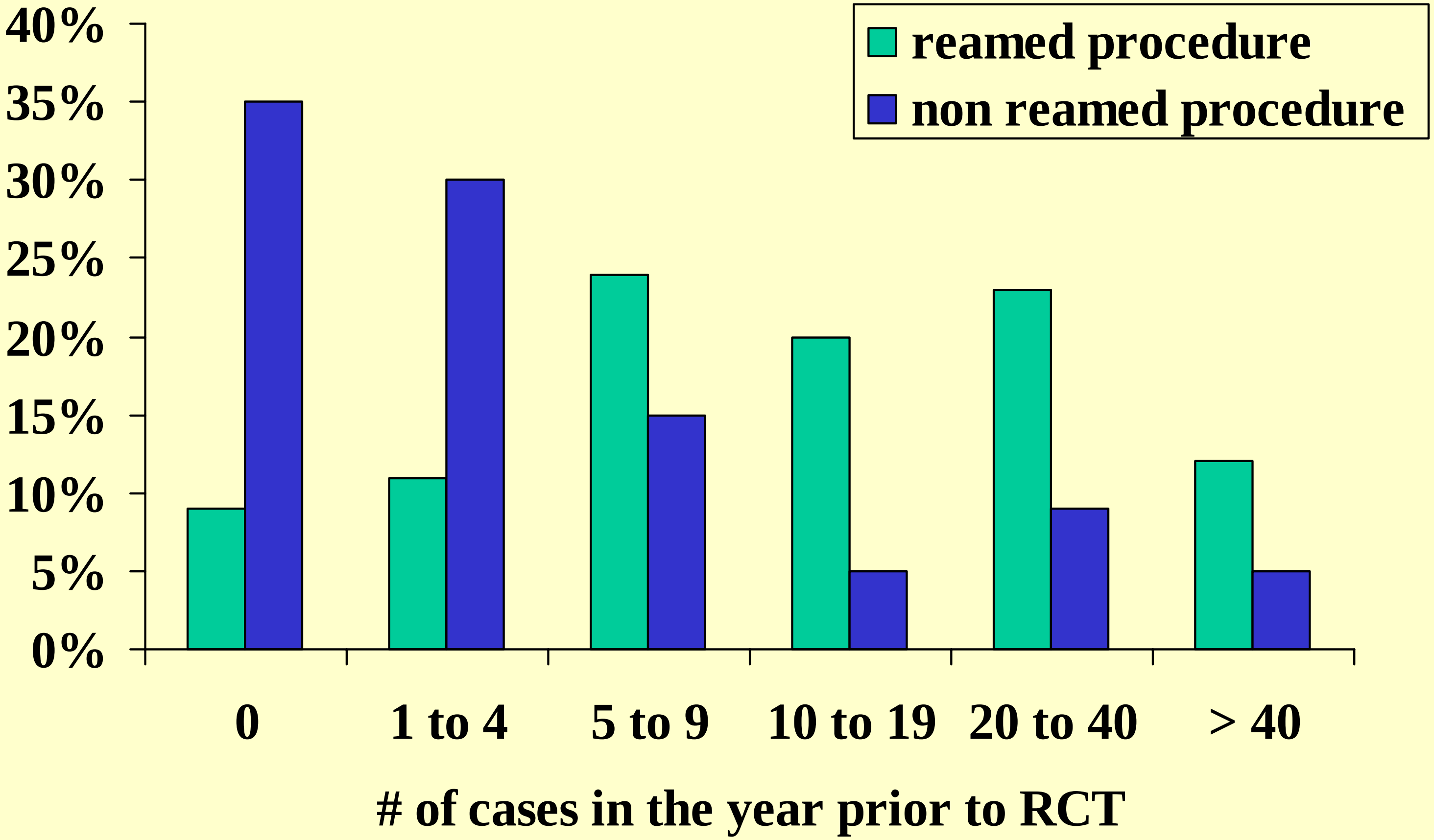
- 140 surgeons from Canada, US, and Netherlands
- 1350 patients
- Patients randomised to reamed or unreamed nails
- Expertise and preferences were assessed for surgeons at start of study

Clinician preferences in SPRINT

Survey of SPRINT surgeons

- prior to trial
  - 87% thought reamed procedure was superior
  - 86% moderate to extremely confident
- after 900 patients had been randomized (but results still not revealed)
  - numbers unchanged

Surgeon experience prior to SPRINT



SPRINT: study design

- Conventional RCT design was used
- Expertise was assessed for a subset of surgeons
    - This allows us to estimate expected outcomes if EB design had been used, and to evaluate study efficiency
- Outcome: SF-36

SPRINT study design…

Various definitions of "expert" are possible…

- we used > median number of reamed procedures done during and after specialty training
- we counted expertise on <u>either</u> technique as relevant

Potential disadvantages of EB design

- Loss of statistical efficiency
  - Clinicians are nested in treatment groups
- Treatment effect may be <u>smaller</u> than conventional RCT
  - Skilled clinicians may be the ones delivering the inferior treatment

Potential disadvantages of EB design

- Clinician effects
  - Should clearly take them into account if clinicians are nested in treatment groups
  - Should also be taken into account even if clinicians are crossed with treatments (as in conventional design)
    - But this is <u>rarely</u> done!

Model development

Outline –

1. Create ANOVA approach for EB and conventional designs
2. Identify treatment effect estimates and SE's
3. Compare two approaches for relative efficiency

[We will first consider the simpler case of perfectly balanced designs for illustration]

Model development

<u>EB design</u>:
- k surgeons / treatment group
- m patients / surgeon

<u>Conventional design</u>
- k' surgeons (total)
- m' patients / surgeon in <u>each</u> treatment group

Total patients: $2km$ (EB design)
$2k'm'$ (conventional)

Model

Response for treatment group *t*, surgeon *i*, patient *j* :

$$Y_{tij} = \mu + \alpha_t + \beta_{ti} + \varepsilon_{tij}$$

Surgeon effect (β) random:

- <u>crossed</u> with treatment (conventional design)
- or <u>nested</u> in treatment (EB design)

- var(β) = σ_S^2 ; var(ε) = σ^2
- Treatment effect: $\alpha = \alpha_1 - \alpha_2$
- Estimate: $\hat{\alpha} = \bar{Y}_{1\cdot\cdot} - \bar{Y}_{2\cdot\cdot}$

Conventional Design

Source	Df	SS	MS	E(MS)	F
Treatment	1	SST	SST	$\sigma^2 + k'm'\sum\alpha_t^2$	MST/ MSE
Surgeon	k′-1	SSS	SSS/ (k′-1)	$\sigma^2 + 2m'\sigma_S^2$	MSS/ MSE
Error	k′(2m′-1) -1	SSE	SSE/ k′(2m′-1) - 1	σ^2	
Total	2k′m′-1	SSTL			

[Surgeon effect random, no interaction]

EB Design

Source	df	SS	MS	E(MS)	F
Treatment	1	SST	SST	$\sigma^2 + m\sigma_S^2 + km\sum\alpha_i^2$	MST/ MSS
Surgeon	2(k-1)	SSS	SSS/ 2(k-1)	$\sigma^2 + m\sigma_S^2$	MSS/ MSE
Error	2k(m-1)	SSE	SSE/ 2k(m-1)	σ^2	
Total	2km-1	SSTL			

[Surgeon effect random, no interaction]

Study efficiency

Conventional design:

$$\mathrm{var}(\hat{\alpha}) = \frac{2\sigma^2}{m'k'}$$

EB design:

$$\mathrm{var}(\hat{\alpha}) = \frac{2}{mk}\left[\sigma^2 + m\sigma_S^2\right]$$

Relative efficiency:

$$\mathrm{var}_{EB}(\hat{\alpha}) / \mathrm{var}_C(\hat{\alpha}) = \frac{m'k'}{mk}\left[1 + m\sigma_S^2 / \sigma^2\right]$$

$$= 1 + m\sigma_S^2 / \sigma^2$$

(Assuming same total number of patients)

Study effect size

Conventional design:

$$E(\hat{\alpha}) = \alpha_1 - \alpha_2$$

EB design:

$$E(\hat{\alpha}) = (\alpha_1 - \alpha_2) + (B_1 - B_2)$$

where $B_t = \frac{1}{k}\sum_{i=1}^{k} \beta_{ti}$ (average expertise effect in treatment group t)

Study effect size…

If expertise can be characterised: (e.g. above/below median # of patients treated with study intervention)

then $$E(B_t) = \sum_m \pi_{tm} \gamma_{tm}$$

where:

$\{\pi_{tm}\}$ defines expertise distribution of surgeons using *t* in groups m
and

γ_{tm} is the expertise effect in group m

SPRINT…1: sample sizes

- 596 patients; 76 surgeons (k')

  (subset where surgeon expertise was known)
- Mean # pts/surgeon per treatment (m')=

  $596 / (76 \times 2) = 3.92$

- Projected EB designs:

  (I) $k = 38$ $m = 7.84$ (same # pts/surgeon)

  (II) $k = 76$ $m = 3.92$ (half # pts/surgeon)

SPRINT…2: results (SF-36)

Estimated treatment effect $(\hat{\alpha})$ = 0.64

Surgeon variance (σ_S^2) = 3.91

Error variance (σ^2) = 90.57

Conventional design: $\mathrm{var}(\hat{\alpha}) = \dfrac{2\sigma^2}{m'k'}$ = 0.61

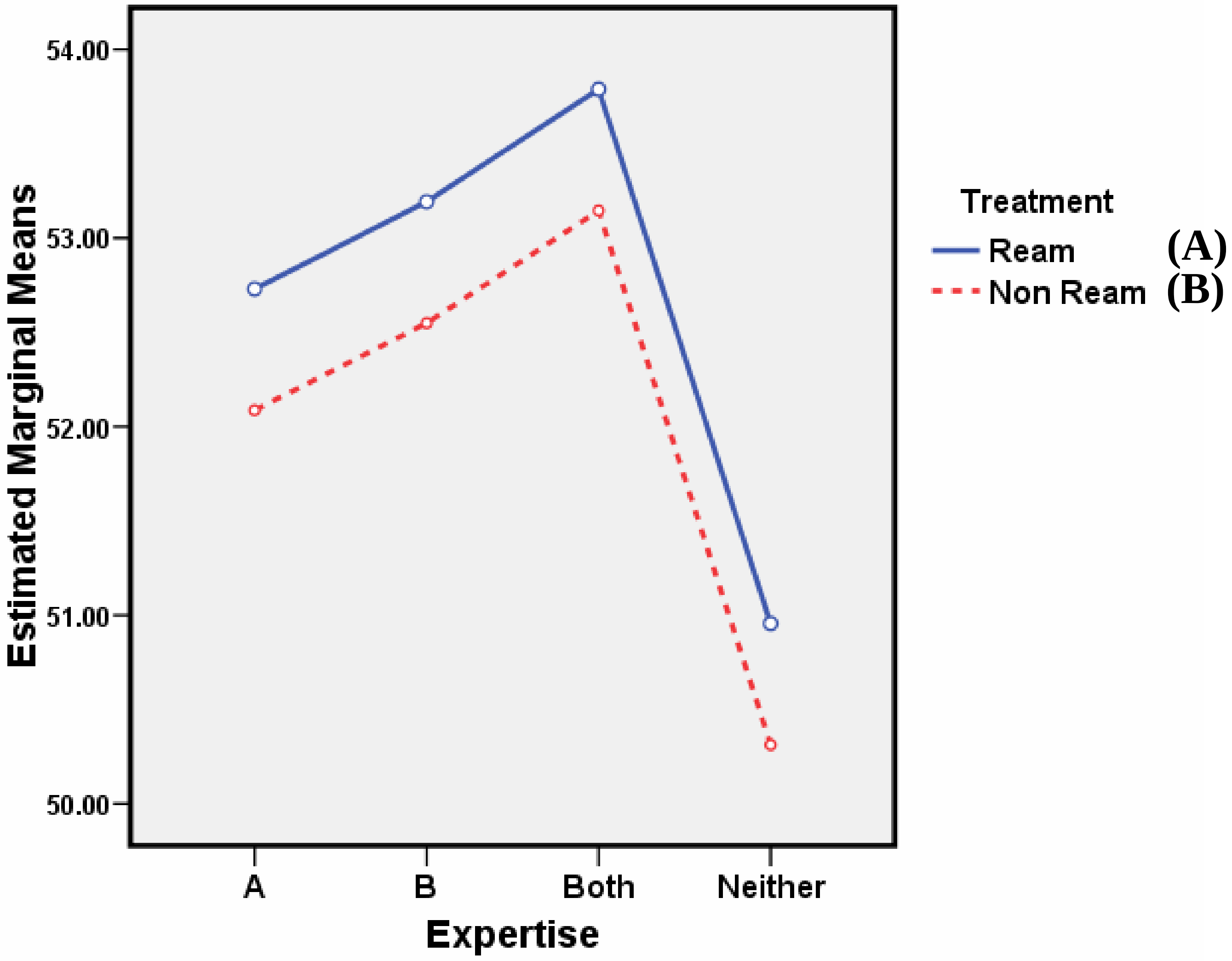
EB-I design: $\mathrm{var}(\hat{\alpha}) = \dfrac{2}{mk}\left[\sigma^2 + m\sigma_S^2\right]$ = 0.81

Relative efficiency: = 1.33 (EB-I, same # pts/surgeon)

[or 1.16 (EB-II, half # pts/surgeon)]

SPRINT…3: expertise effect

SF-36



SPRINT…4: projected EB results

Estimated effects of expertise:

- Expert in A and B	2.83
- Expert in A only	1.78
- Expert in B only	2.24
- Expert in neither	0

Expected expertise effect in EB design:

<u>A-arm</u>	½ (2.83 + 1.78)	= 2.31
<u>B-arm</u>	½ (2.83 + 2.24)	= 2.54
<u>Net</u>	2.31 – 2.54	= -0.23
<u>Effect size</u>	0.64 – 0.23	= 0.41

(assumes uniform distribution of expertise)

SPRINT…5: EB vs. conventional

	Effect	SE	Effect/SE	Ratio
Conv	0.64	0.61	1.05	1.00
EB-I	0.41	0.81	0.51	0.49
EB-II	0.41	0.71	0.58	0.55

Discussion

- Expertise-based RCTs may reduce both bias and ethical concerns
- Loss of efficiency because of nested clinician effect
  - This may or may not be counteracted by larger treatment effect

Discussion…EB implementation

- EB design needs to have 2 clinicians available for each patient
  - OK for elective surgery, harder for emergencies
  - Easier to implement EB in larger clinical centres
  - May limit generalisability
  - Patients have to deal with more than one clinician
  - But conventional design would also have problems in small centres if clinician effects exist

Discussion…EB efficiency

In SPRINT, EB analysis had larger standard error and smaller treatment effect

- This is not always true (in other cases, expertise advantage may benefit the superior treatment)

Discussion…interpretation of expertise effect

We adjusted the effect of treatment for surgeon expertise

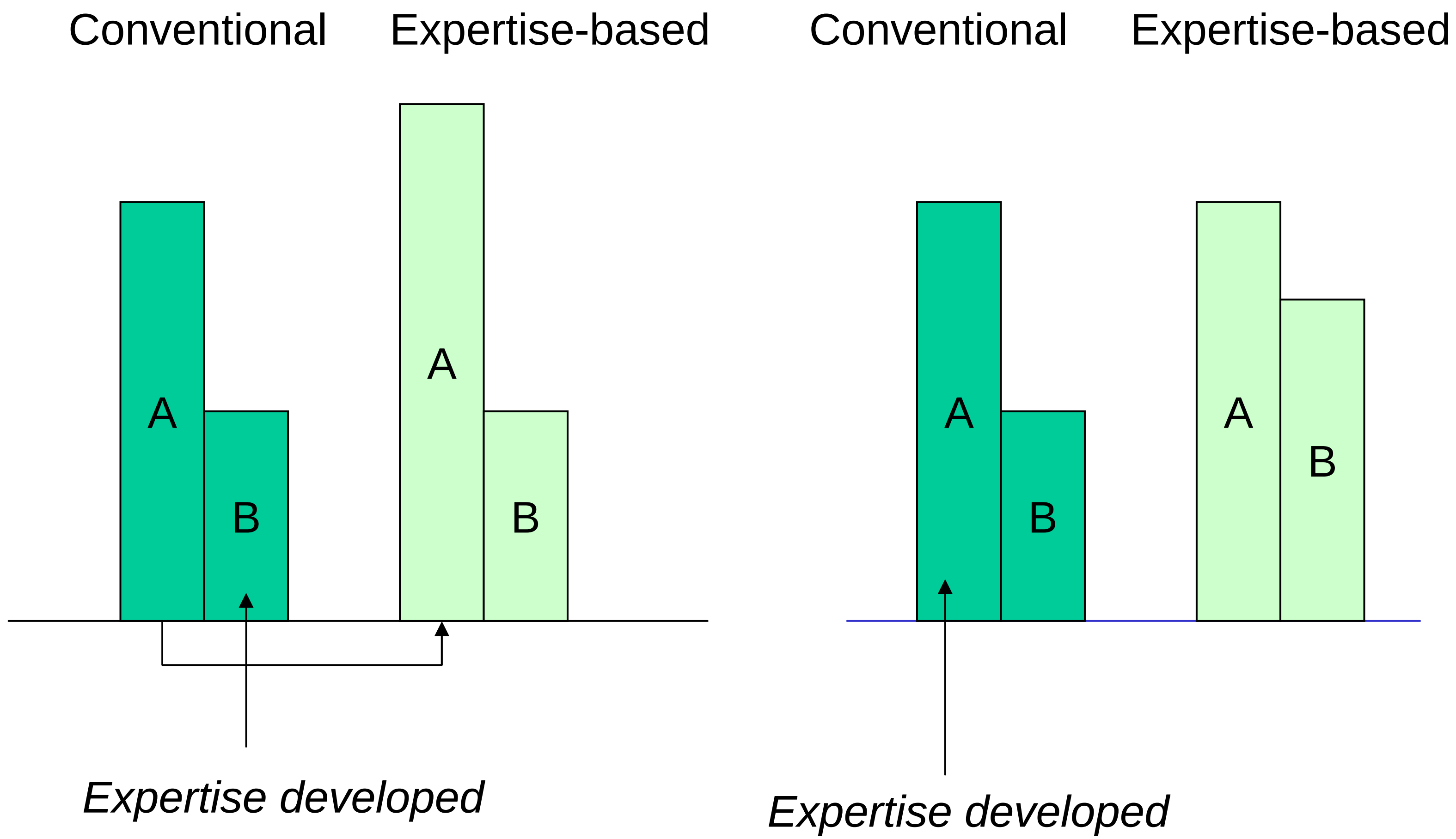
- gives an <u>efficacy</u> interpretation (expected outcomes under ideal circumstances – here, expert surgeons)
- In SPRINT, <u>all</u> expertise effects were beneficial
- This is further justification for considering EB design in the future

Discussion…interpretation of expertise effect

Treatment effect unadjusted for expertise could be thought of as effectiveness:

= expected outcomes in routine practice, with expert or non-expert clinicians

Discussion…implications for clinical training



Discussion…implications for clinical training

Adjustment for expertise decreases treatment effect

Adjustment for expertise increases treatment effect

More training on <u>inferior</u> treatment

More training on <u>superior</u> treatment

Discussion…definitions of expertise

- We counted experience on either technique
  - (idea – experience on one benefits the other)
  - Alternative: count experience only on technique used for particular patient
- We could count experience:
  - In residency / since training / recently / cumulative
  - But differential expertise effects potentially exist with all these definitions

Discussion…clinician by treatment interactions?

- With sufficient data, these <u>can</u> be estimated in the conventional design
- They are <u>not</u> estimable in the EB design
- In SPRINT, these effects were unimportant

For more details…

Statistical issues in the design and analysis of expertise-based randomized clinical trials

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Walter et al., Stat Med 27, 6583-96, 2008