Efficient recruitment strategies in randomised controlled trials with continuous outcomes

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Outline

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- Variance decomposition
- Assumptions
- Efficient recruitment strategies
- Example: atopic dermatitis in infants
- Simulation study results
- Summary and conclusions

Sample size planning in RCTs

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informing

Variance decomposition

Group sample size: $n = \frac{2\sigma^2 (Z_\beta + Z_{\alpha/2})^2}{\Delta^2}$

Define: Y a continuous outcome variable

T a binary treatment variable

X a categorical subgroup variable with levels $j=1,\ldots,k$

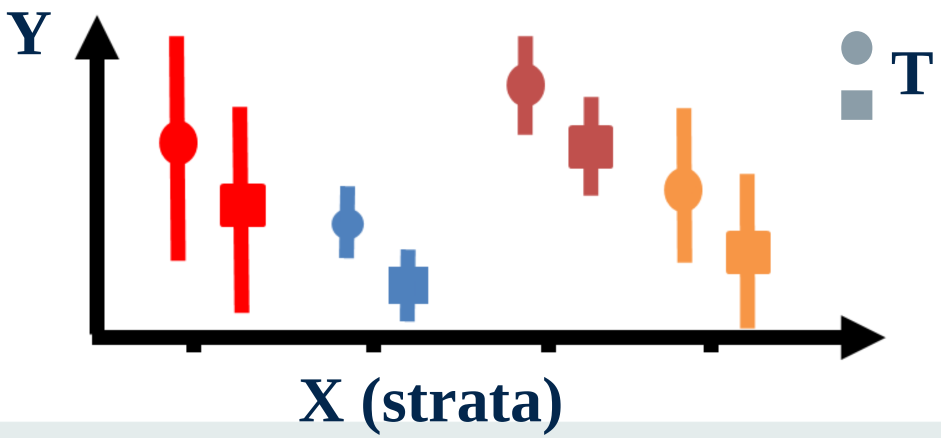
$$\sigma_t^2 = \underbrace{Var(E[Y|X,T=t])}_{\text{between group variation}} + \underbrace{E(Var[Y|X,T=t])}_{\text{(expected) within group variation}}$$

$$= \sum_{j=1}^{k} p_{jt}(\mu_{jt} - \mu_{.t})^2 + \sum_{j=1}^{k} p_{jt}\sigma_{jt}^2$$

with $\mu_{.t} = \sum_j^k p_{jt}\mu_{jt} \quad p_{jt} = \Pr(X = j|T = t)$

Assumptions

- continuous outcome ***Y*** (effect estimate: difference in means)
- ***X*** constitutes a stratification variable (predictor for ***Y***), rand. within levels of ***X***
- effect homogeneity across the ***k*** strata: $\Delta_j = \Delta$ for $j=1,\ldots,k$
- variance heterogeneity across strata: $\sigma_i \neq \sigma_j$ for at least one strata pair $\{ i, j \}$
- $p_{jt} = \Pr(X = j | T = t) = \Pr(X = j) = p_j$; $\tau_j^2(p) := (\mu_{jt} - \mu_{.t})^2$



Efficient recruitment strategies

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Minimise the following function (representation of the common variance):

$$f(p_1, \dots, p_k) = \sum_{j=1}^{k} p_j \tau_j^2(p) + \sum_{j=1}^{k} p_j \sigma_j^2$$

Considering $k+1$ constraint functions:

$$g_0(p_1, \dots, p_k) = \sum_{j=1}^{k} p_j = 1$$

$$g_j(p_j) = 0 < l_j \leq p_j \text{ for } j = 1, \dots, k$$

l_j *ensures minimum representation of* $X = j$

optimum strategy = argmin $f(p_1, \dots, p_k | g_0, g_j, l_j, j = 1, \dots, k)$

Efficient recruitment strategies

- there might exist more than one optimum solution
- variance / sample size savings may only differ marginally between a number of strategies
- some recruitment strategies are preferred / easier to follow than others
- the function arguments are strata sample proportions: depending on the total sample size, over precision is point less

Ideally:

- overview of all possible recruitment strategies: selection of most efficient and best feasible alternatives

Good news:

- number of strata k commonly small
- if we use discrete scale for p_j (e.g. 0.1, 0.2,…, 0.9), prob. dist. constraint g_0 reduces number of possibilites e.g. 36 for k=3, 80 for k=4 and 126 for k=5

Example data: atopic dermatitis

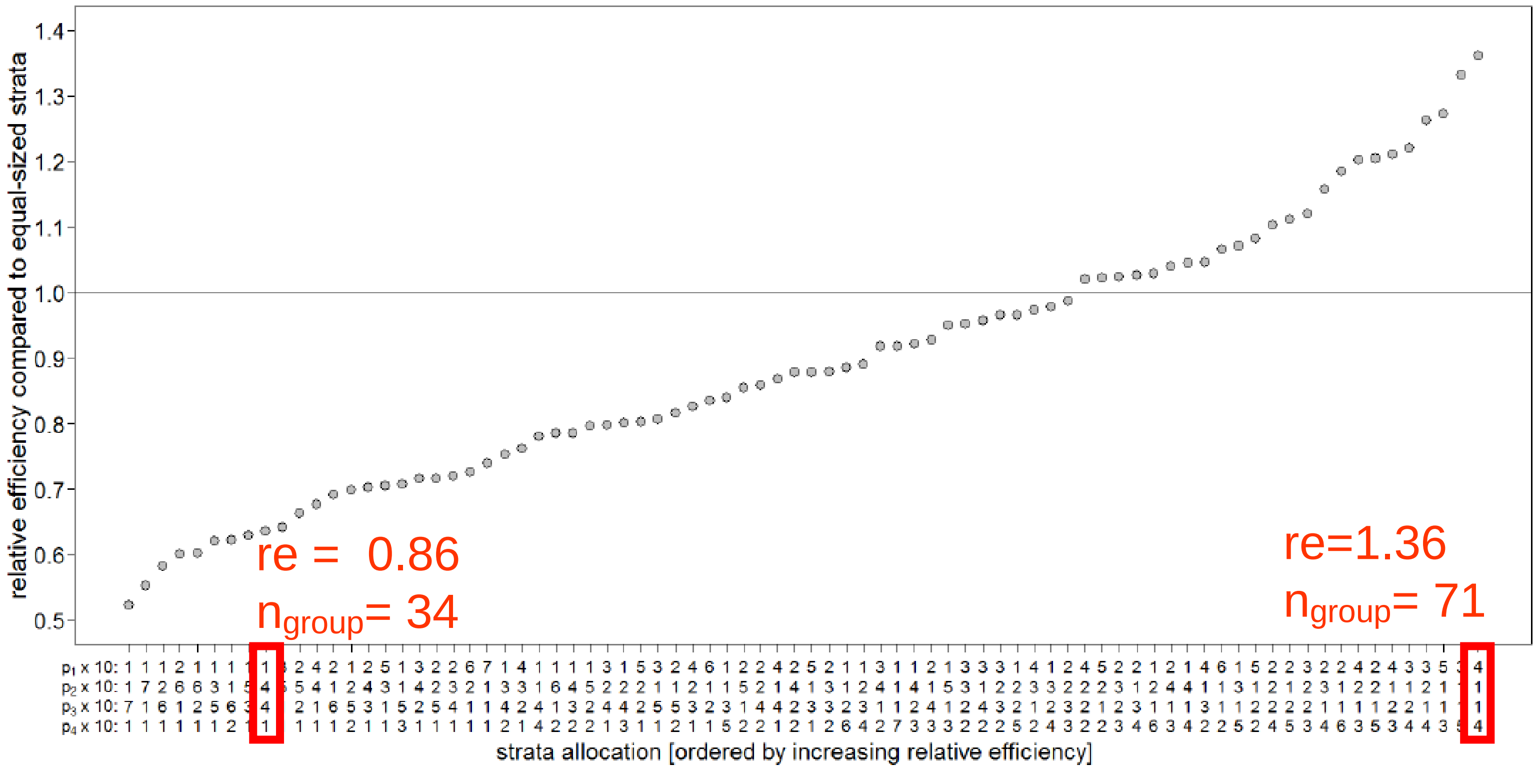
Grueber et al. *Allergy* 2007; 62 (11) : 1270-1276.

Stratum no. (*j*)		Estimated group means (standard deviations) in the four study strata
1	Baseline SCORAD index ≤ 25 & no use of rescue medication	15 (1.5)
2	Baseline SCORAD index ≤ 25 & use of rescue medication	20 (3)
3	Baseline SCORAD index > 25 & no use of rescue medication	29 (3)
4	Baseline SCORAD index > 25 & use of rescue medication	36 (4)
	Total	25 (9)

standard sample size calculation

$\sigma=9$; $\Delta=5$;
$\alpha=0.05$; $\beta=0.20$
→ $n_{group}=52$

Example data: atopic dermatitis



Example data: atopic dermatitis

adjustment for strata variables

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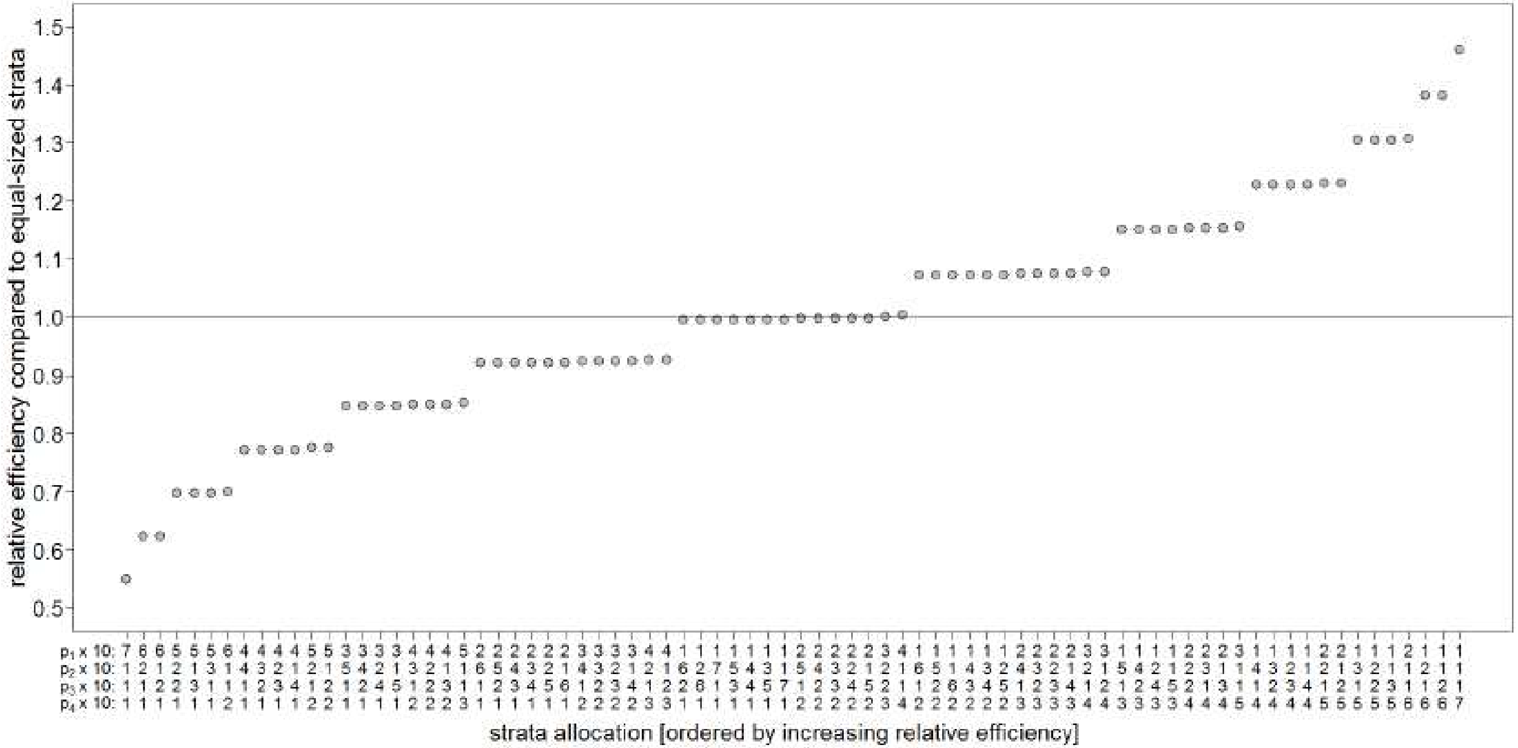

Simulation study results

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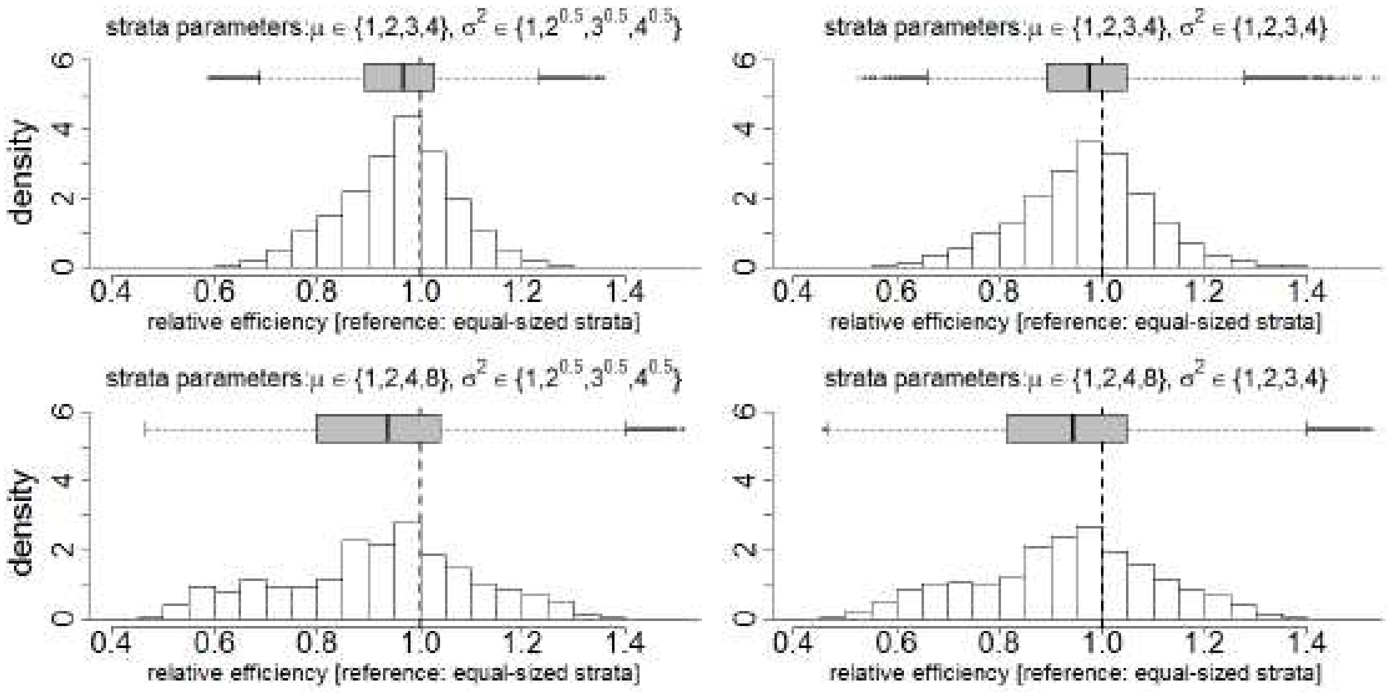

Summary and conclusion

- strata representation matters
- given effect homogeneity assumption (scale dependent!) strata allocation can be efficiently chosen: maximising precision of the effect estimate / minimising sample size
- outcome statistics (not only effect estimates) should be reported for stratification factor levels

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Thank You