

A decision-theoretic value-of-information approach to the design of clinical trials in small populations

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Conventional clinical trial design and interpretation:

fix type error rates

due to concern about consequence of error

Alternative idea:

compare decisions in terms of – gains to patients

– costs of observations

Big n : high prob. correct decision, high cost, few patients benefit

Small n : low prob. correct decision, low cost, more patients benefit



Gains:

- to patients receiving C

- to patients receiving E (for unknown treatment effect)

Costs:

- fixed cost of trial

- extra cost per patient in trial

- extra cost for patients receiving E

These need to be on same scale

Choose optimal n and α



Example – trial in haemophilia A

Trial cost: $\$1,000,000 + \$5,000/\text{patient}$

Additional cost for new treatment: $\$61,000$

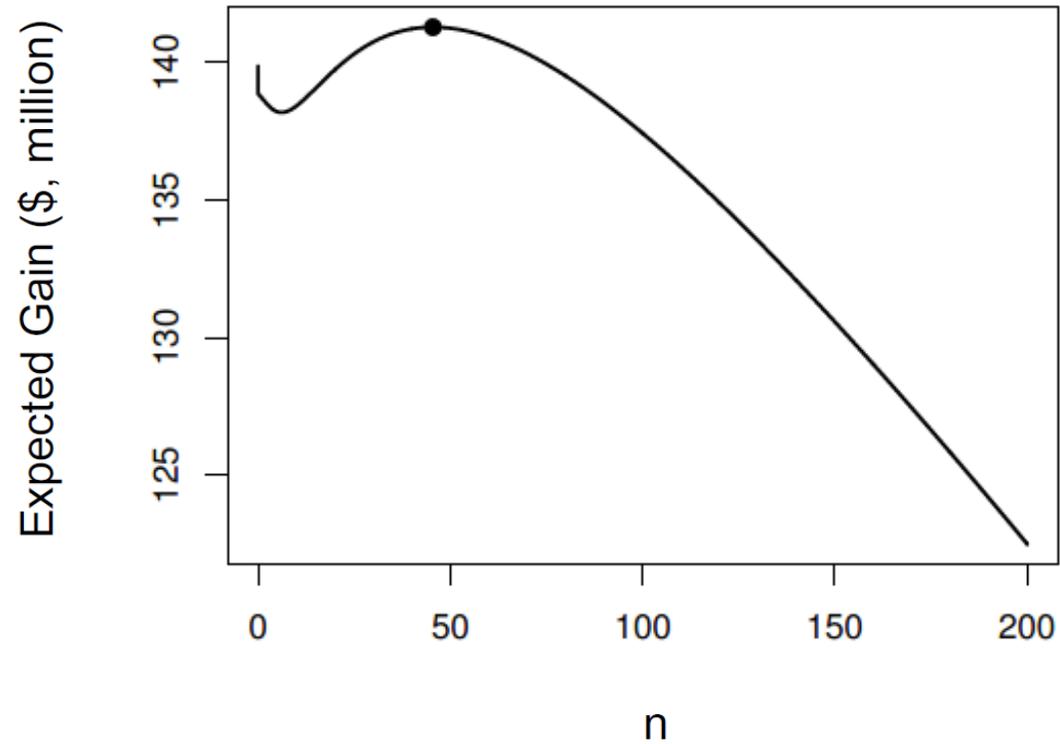
Prior for difference in probability of treatment success:
mean = 0.24, s.d = 0.12

Monetary value per treatment success $\$400,000$

Population size: $N = 4,000$

$n/2$	$n/2$	
$4n$		$4000 - 5n$

Design optimization

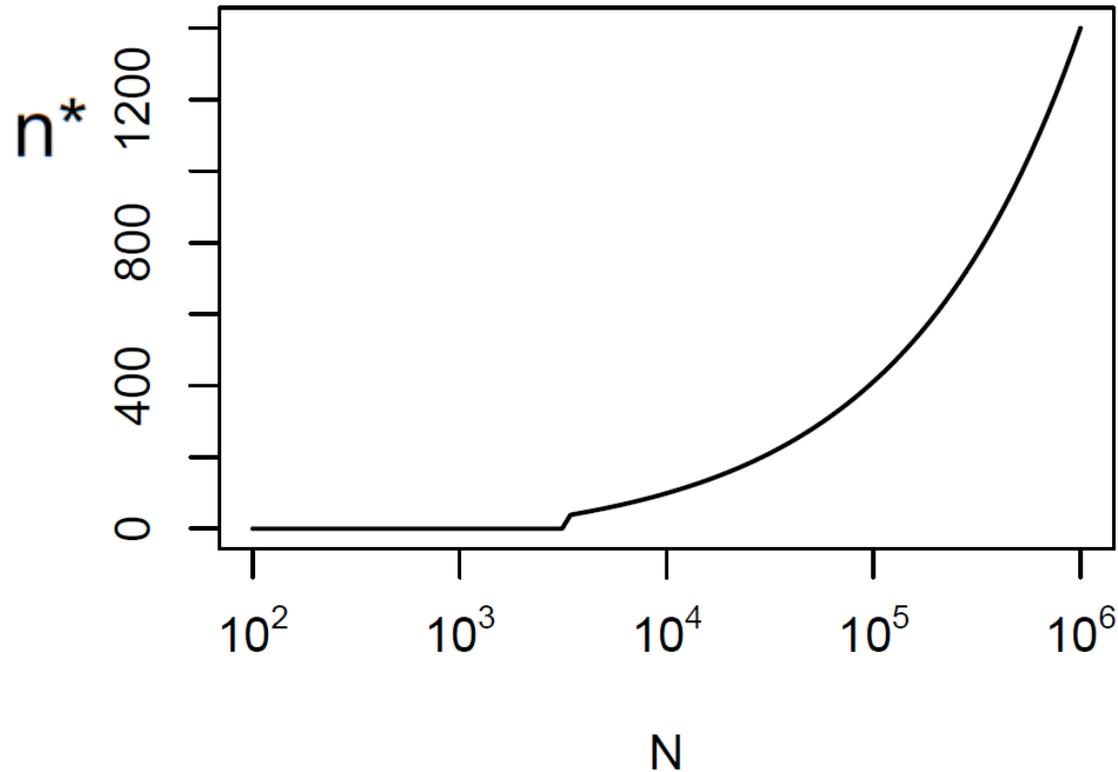


Optimal design has $n = 46$ (23 per arm)

$$\alpha = 0.35$$



Effect of population size – (i) on optimal trial sample size

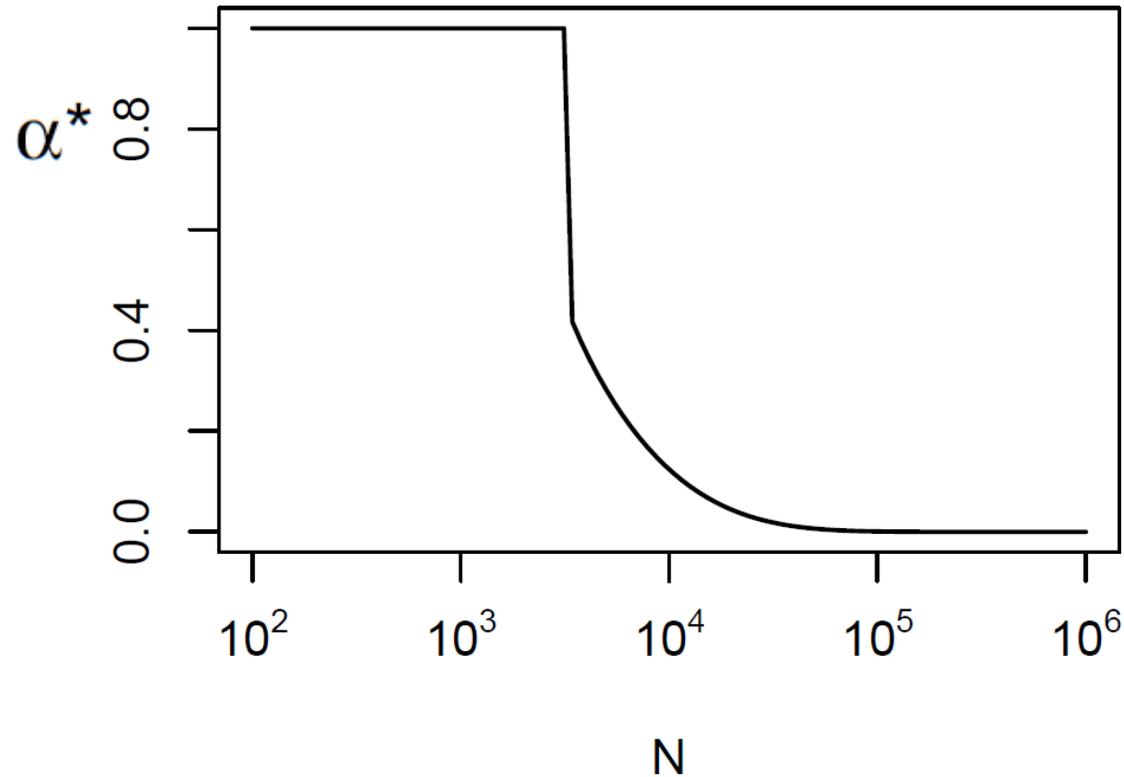


Optimal sample size increases with population size:

$$n \propto N^{1/2} \text{ for large } N$$

For small N optimal to approve new treatment without a trial

Effect of population size– (ii) on optimal significance level



Optimal α decreases with population size:

small N : $\alpha > 0.05$

large N : $\alpha < 0.05$

Decision reflects population size

Discussion

Trials in rare diseases do currently use smaller sample sizes

Value-of-information methods

- could formalise ad-hoc sample size choice

- modify sample size according to population size by
considering value of information gained

- lead to clinical decision-making reflecting gain to population

- do not increase information available from small trial

Not the last word; but maybe the start of a conversation

