A value-of-information approach to sample size determination in confirmatory clinical trials in small populations

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InSPiRe
Innovative methodology for small populations research

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Conventional sample size calculation:

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

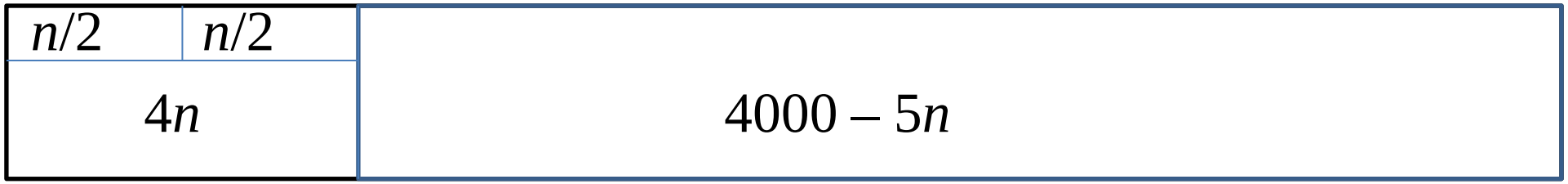
Trial cost: $1,000,000 + $5,000/patient

Additional cost for new treatment: $61,000

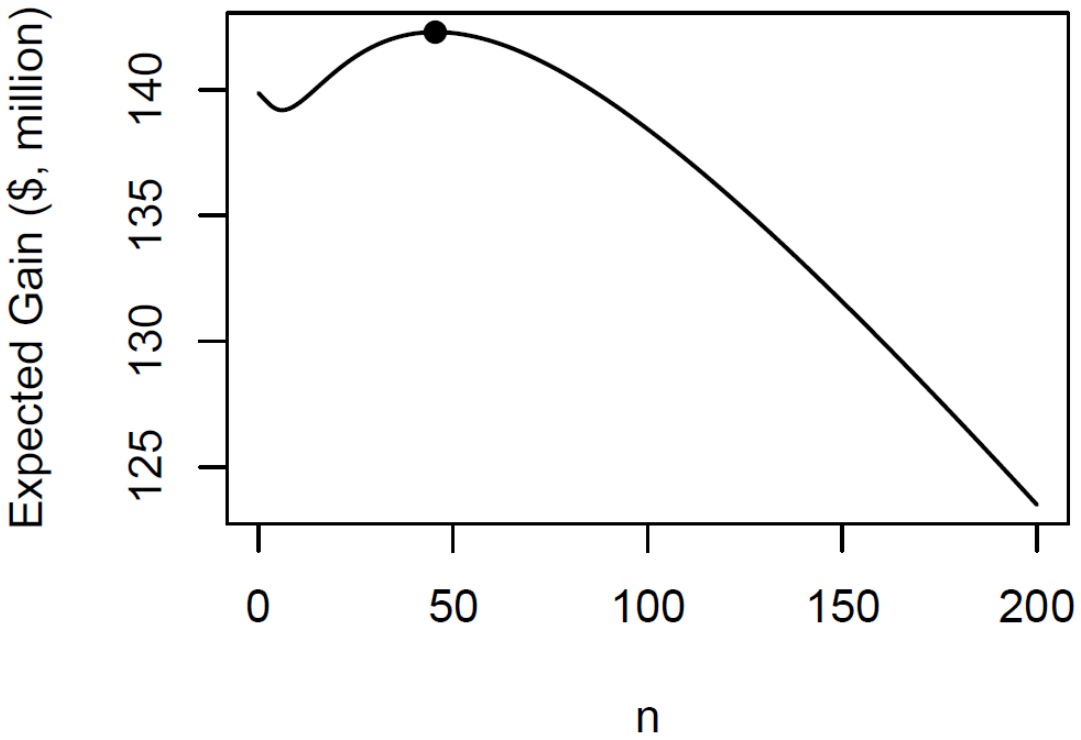
Prior for difference in probability of treatment success:
mean = 0.24, s.d = 0.12

Monetary value per treatment success $400,000

Population size: 4,000



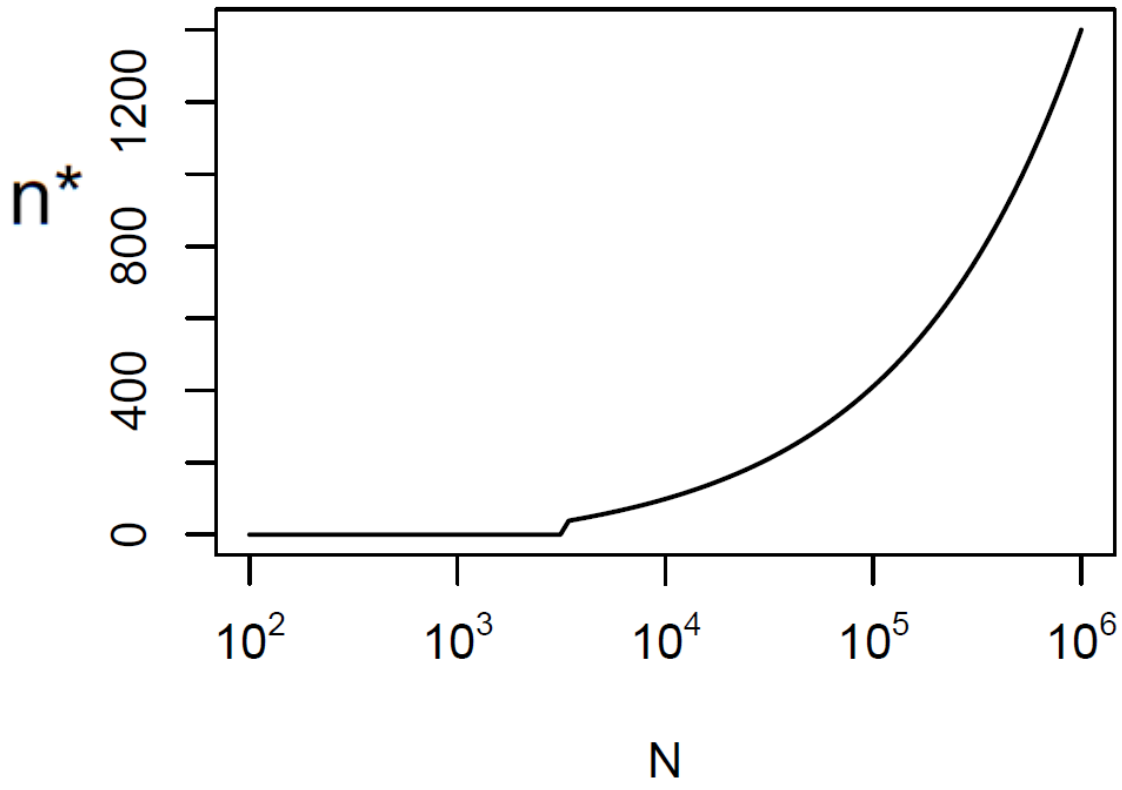
Design optimization

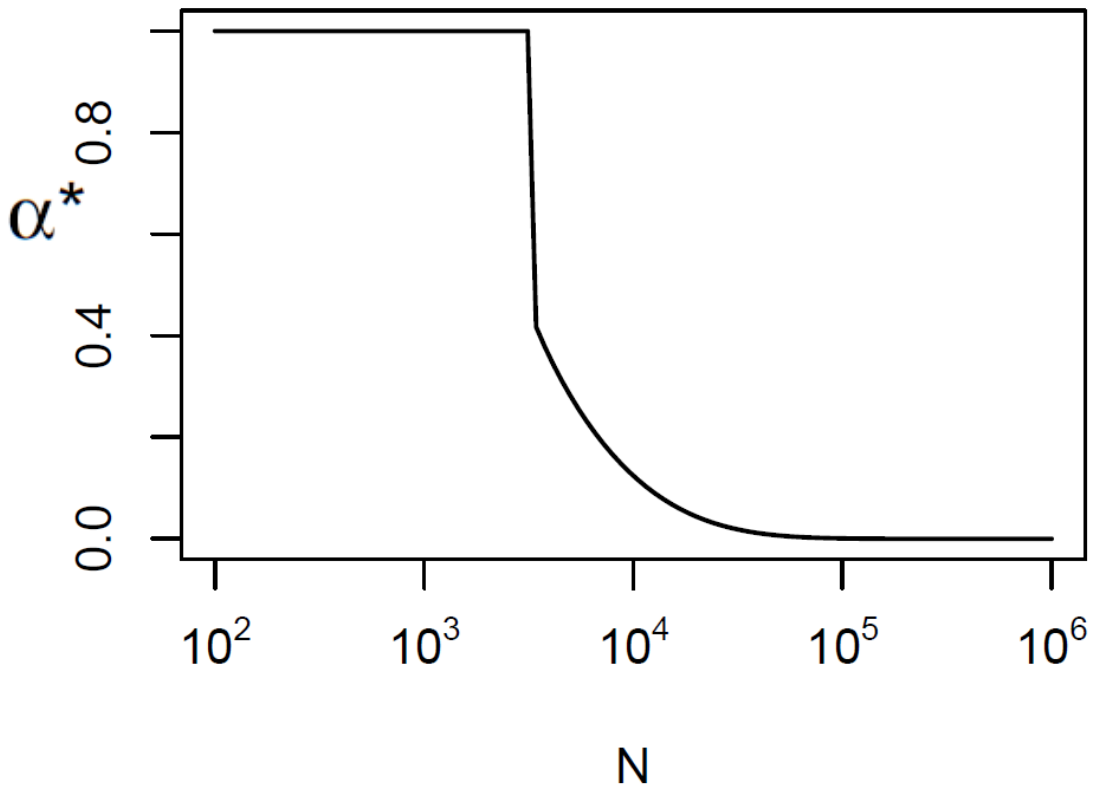


Optimal design has n = 46 (23 per arm)

α = 0.35

Effect of population size





Smaller populations lead to smaller trials and larger α

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
- do not increase information available from small trial

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