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MEDICAL SCHOOL

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

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InSPiRe

Innovative methodology for small populations research

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Levels of evidence requirements in rare diseases

Regulation (EC) 141/2000:

> "*patients with* [rare] *conditions deserve the same quality, safety and efficacy in medicinal products as other patients*"
>
> "*orphan products should therefore be submitted to the normal evaluation process*"

FDA Draft Guidance on Rare Diseases:

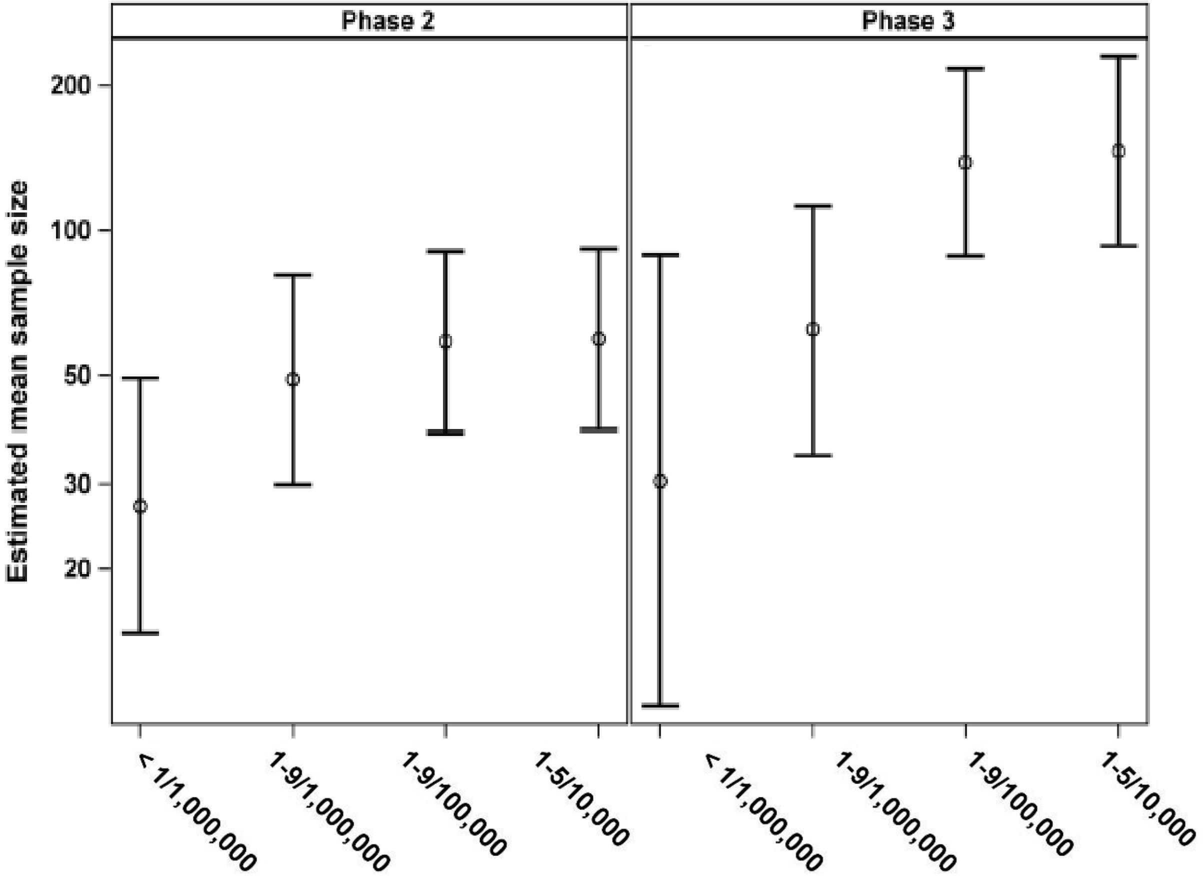
> "*The Orphan Drug Act* […] *does not create a statutory standard* […] *different from* […] *common conditions*"

Sample sizes for rare disease trials from clinicaltrials.gov database

Sample size	Non-rare disease	Rare disease
500+	8%	1%
101 – 500	30%	13%
51 – 100	22%	19%
0 – 50	40%	67%

Bell and Tudur Smith, 2014, *Orphanet J Rare Dis*, 9: 170

For rare diseases grouped by prevalence…



Hee *et al*. 2017, *Orphanet J Rare Dis*, 12: 44

Example of a trial in haemophilia A

E: tailored prophylaxis with recombinant factor VIII

C: usual care

Expected prob. of success on C, $p_C = 0.55$

Expected prob. of success on E, $p_E = 0.79$

Conventional sample size calculation:

type I error rate, $\alpha = 0.05$ (two-sided)

power, $1 - \beta = 0.9$

total sample size, $n = 150$ (75 per arm)

Abrahamyan *et al*., 2014, *J. Gen. Int. Med.*, 29, 767-73

Rare disease: size of total population to be treated = 4000

600 on C		3250
75 on C	75 on E	

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

Additional cost for E: $61,000 per patient

Treatment success value: $400,000 per patient

E(gain) relative to all receiving C: if $p_C = p_E = 0.55$

–$1,000,000 –$5,000×150 –$61,000×3250×0.025

–$61,000×75

= –$11 million

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Additional cost for E: $61,000 per patient

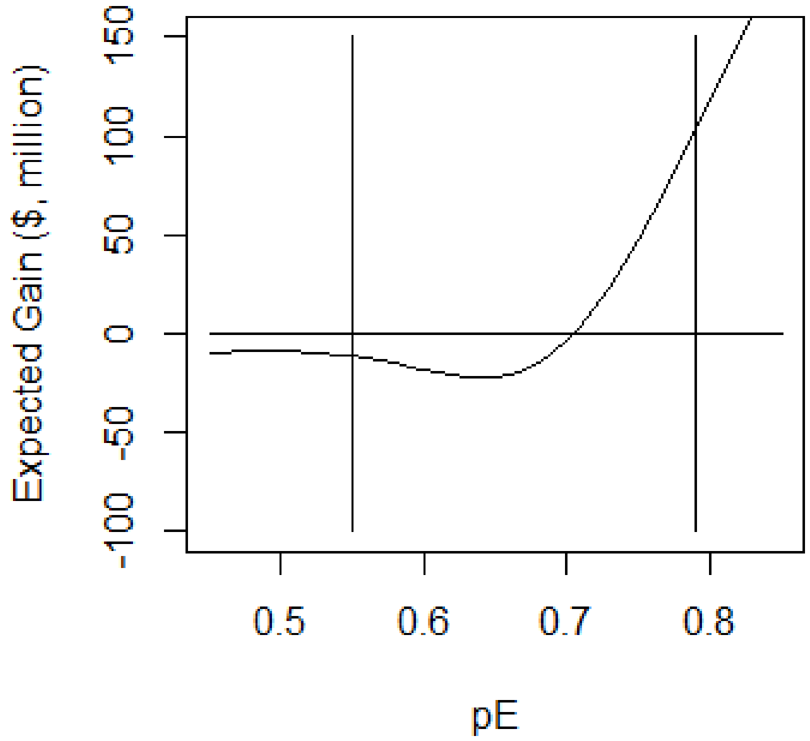
Treatment success value: $400,000 per patient

E(gain) relative to all receiving C: if $p_C = 0.55$, $p_E = 0.79$

–$1,000,000 –$5,000×150 –$61,000×3250×0.9

–$61,000×75 +$400,000×3250×0.9×0.24

+$400,000×75×0.24 = $103 million



Expected Gain ($, million)
150
100
50
0
-50
-100
0.5
0.6
0.7
0.8
pE

Impact of reducing to 80% power:

448 on C		3440
56 on C	56 on E	

E(gain) relative to all receiving C: if $p_C = p_E = 0.55$

–\$1,000,000 –\$5,000×112 –\$61,000×3440×0.025

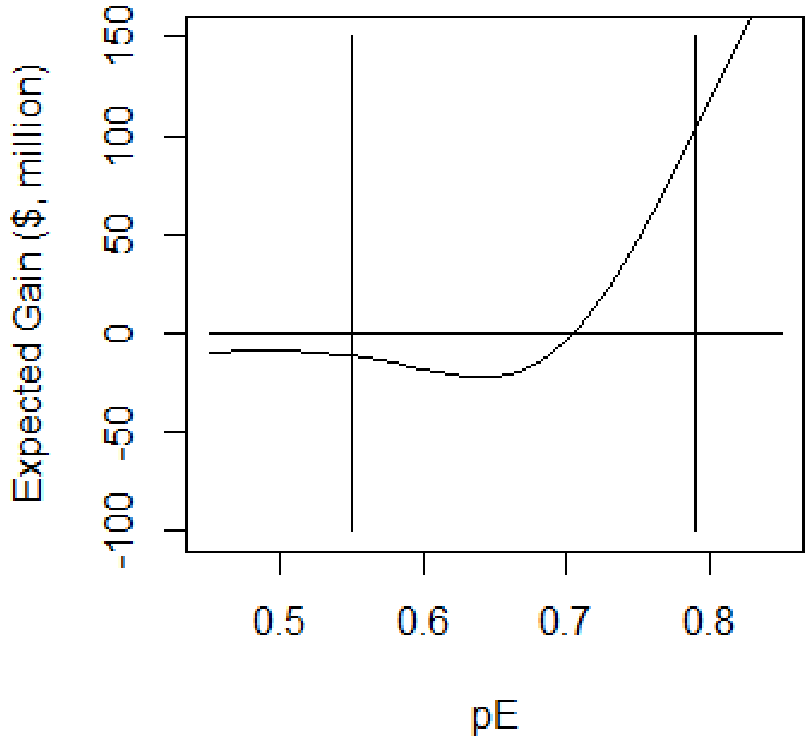
–\$61,000×56

E(gain) relative to all receiving C: if $p_C = 0.55$, $p_E = 0.79$

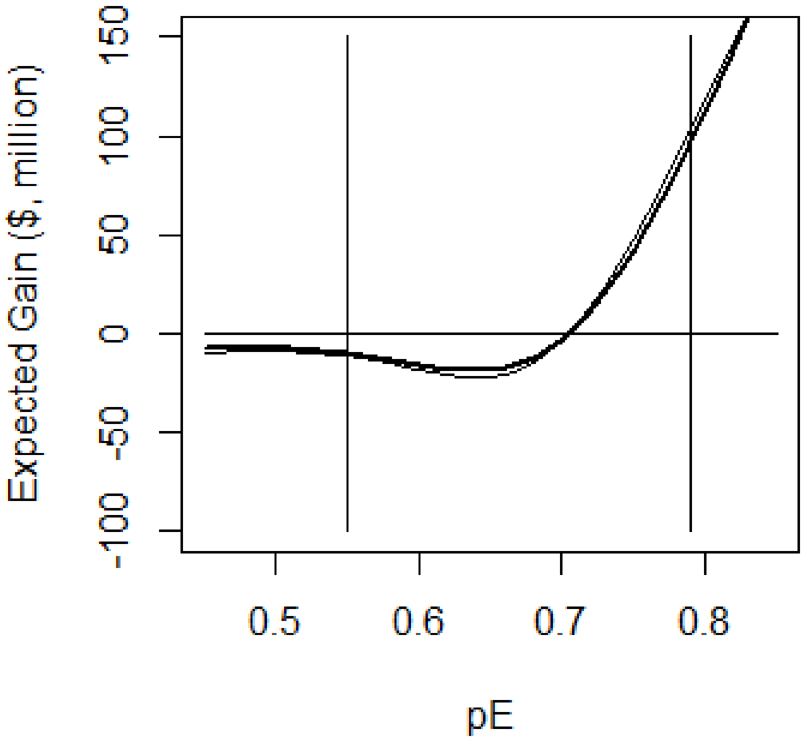
–\$1,000,000 –\$5,000×112 –\$61,000×3440×0.8

–\$61,000×56 +\$400,000×3440×0.8×0.24

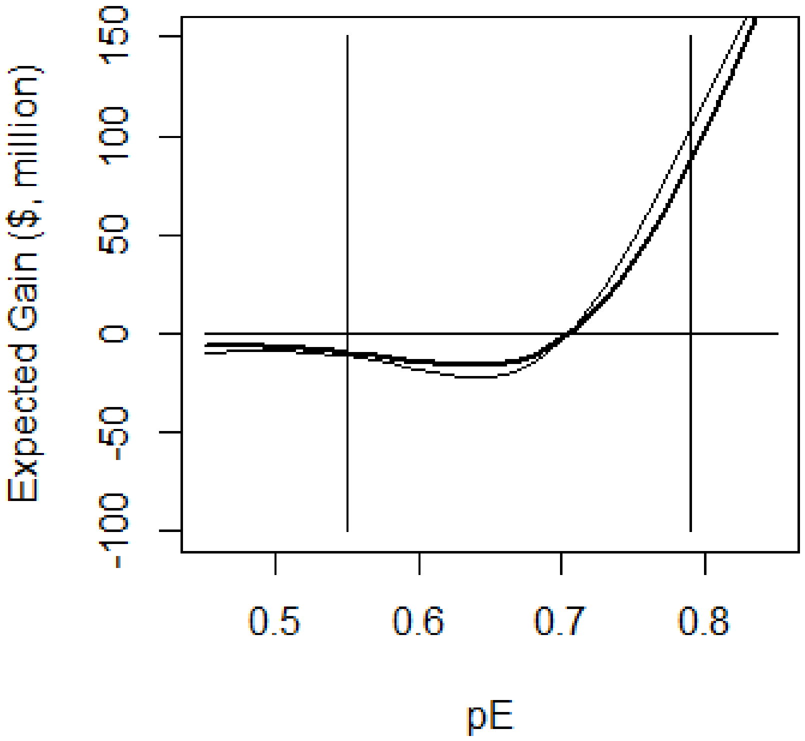
+\$400,000×56×0.24



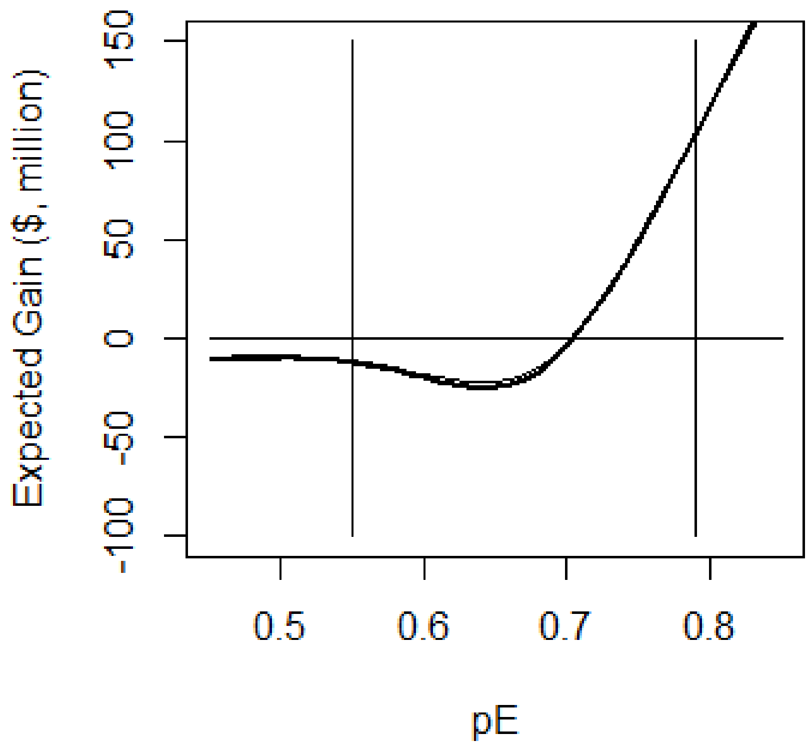
Expected Gain ($, million)
150
100
50
0
-50
-100
0.5
0.6
0.7
0.8
pE



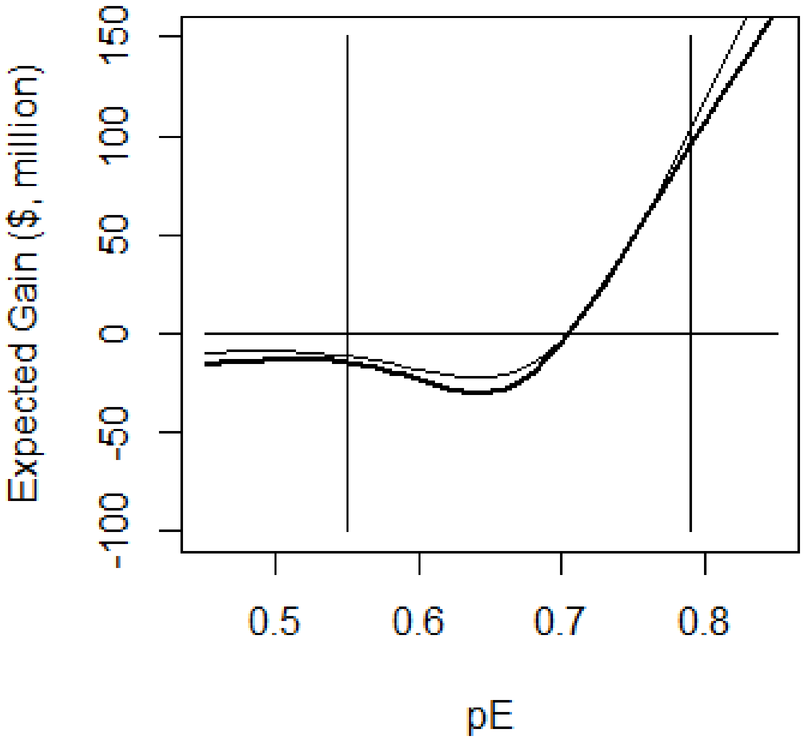
power = 0.8



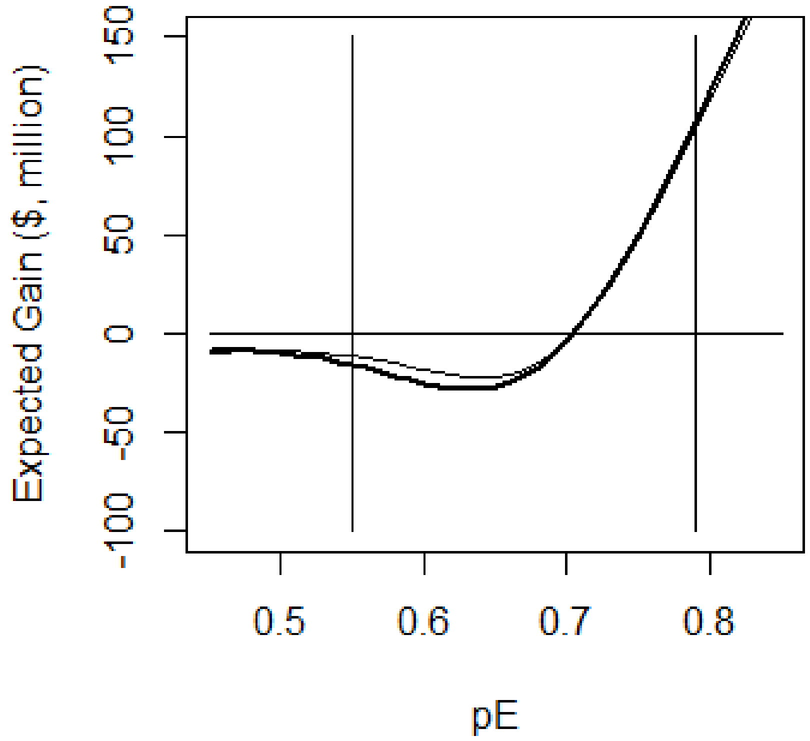
power = 0.7



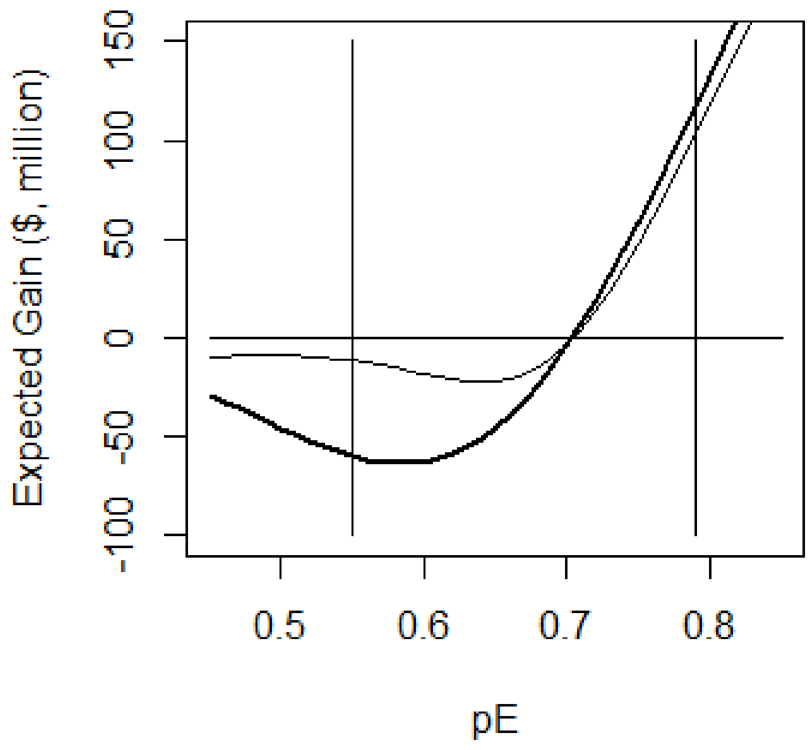
power = 0.95



power = 0.99

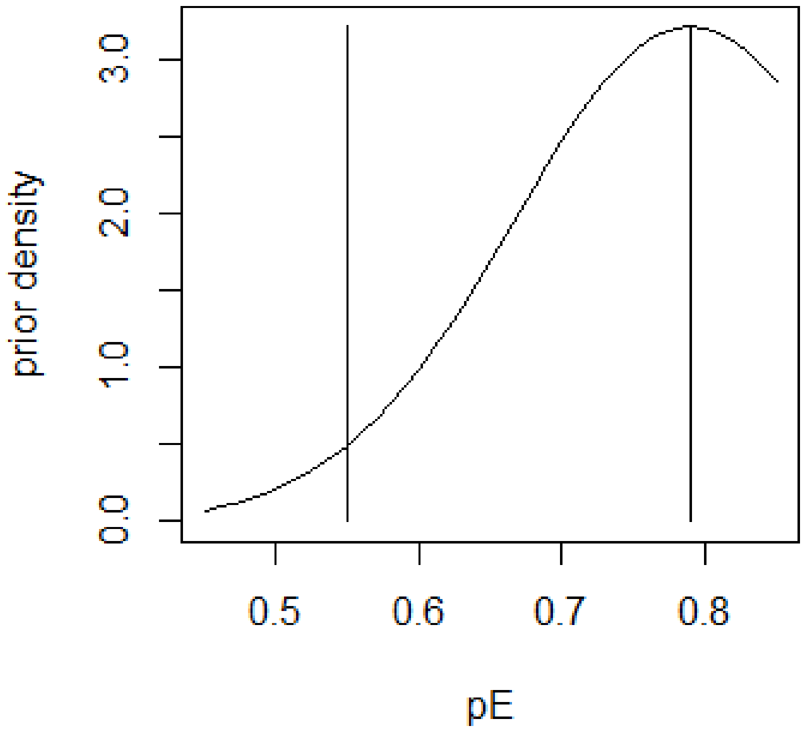


$\alpha = 0.1$

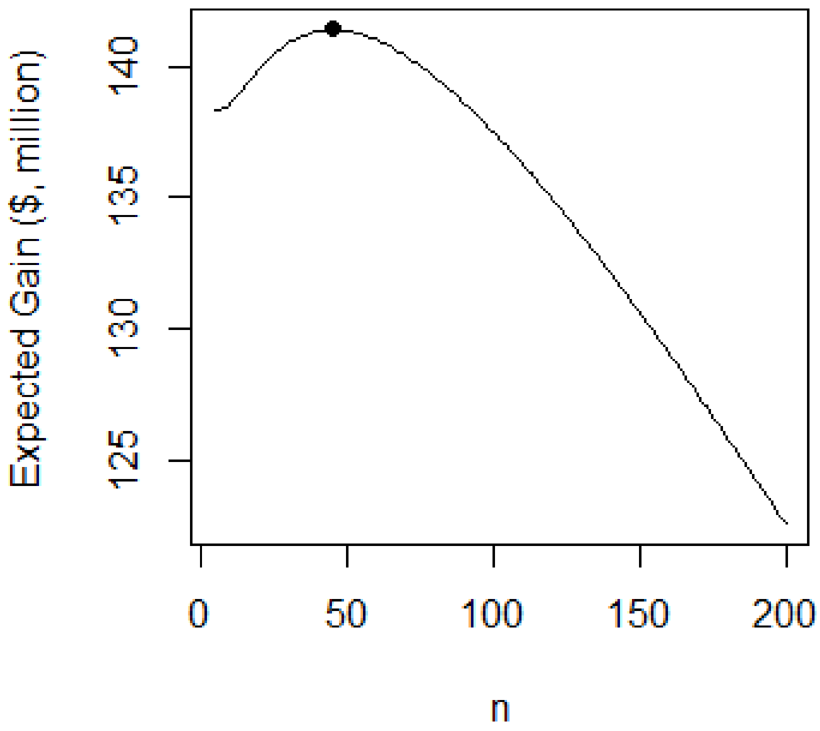


$\alpha = 0.5$

Prior distribution

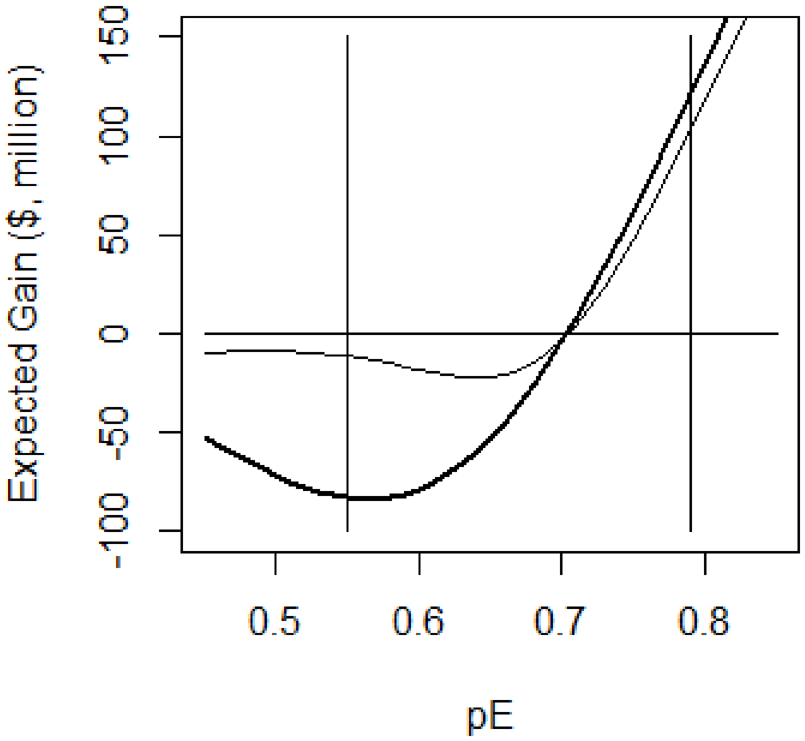


Design optimization: E(gain) for optimal α for range of n



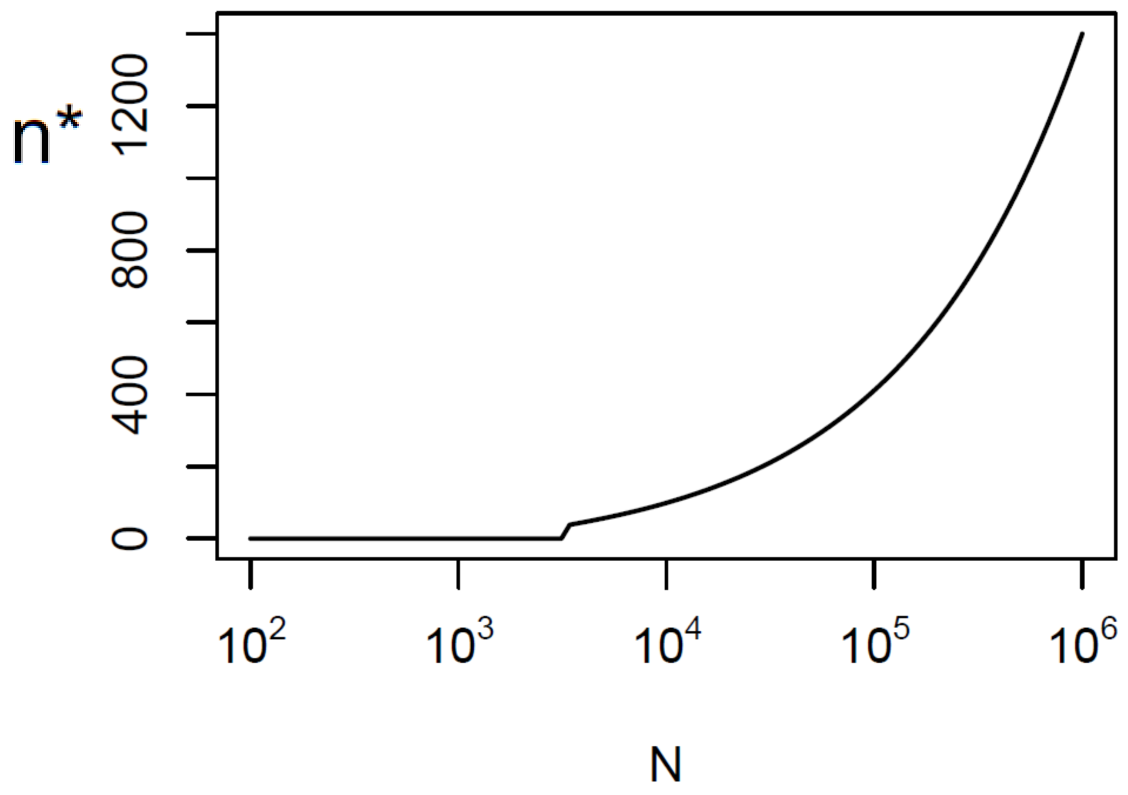
Optimal design has n = 46 (23 per arm)

$\alpha = 0.35$



$\alpha = 0.35$, $n = 46$

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

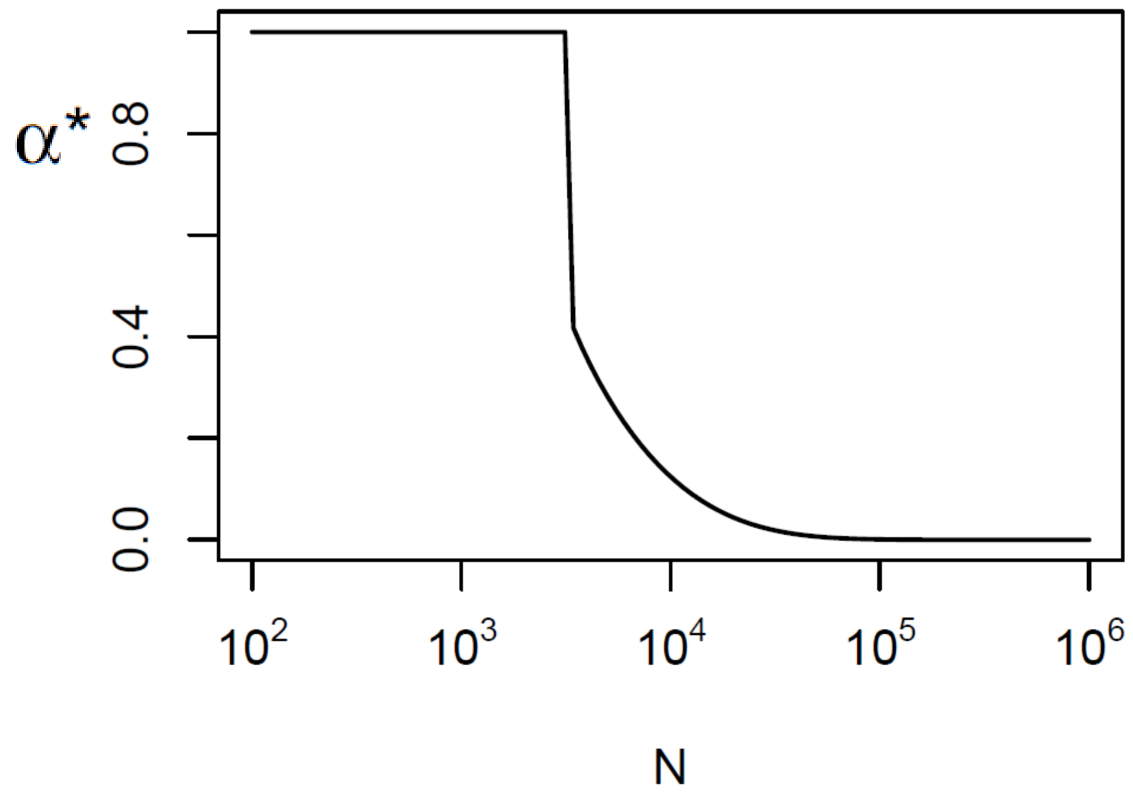


Optimal sample size smaller for smaller population size N:

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

For small N optimal to approve new treatment without a trial!

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



Optimal α larger for smaller population size:

small N: $\alpha > 0.05$

large N: $\alpha < 0.05$

Decision reflects population size

Summary

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 part of a conversation