Decision-theoretic designs for clinical trials in rare diseases/small populations

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Innovative methodology for small populations research

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Small populations

- Paediatric
- Vulnerable
- Stratified/personalized medicine
- Rare disease

Rare diseases

- In the EU: prevalence <5/10,000
  - ~ 254,500 people in the EU (population of 509 million)
- In the US: affects < 200,000
  - ~ 62/100,000

Design for rare disease trials

- May still be able to design a frequentist RCT
- EMA/CHMP “Guideline on clinical trials in small populations” – most orphan indications submitted for regulatory approval are based on RCTs
- Deviation from RCT is uncommon

Buckley (*Lancet*, 2008;371(9629):2051-5)

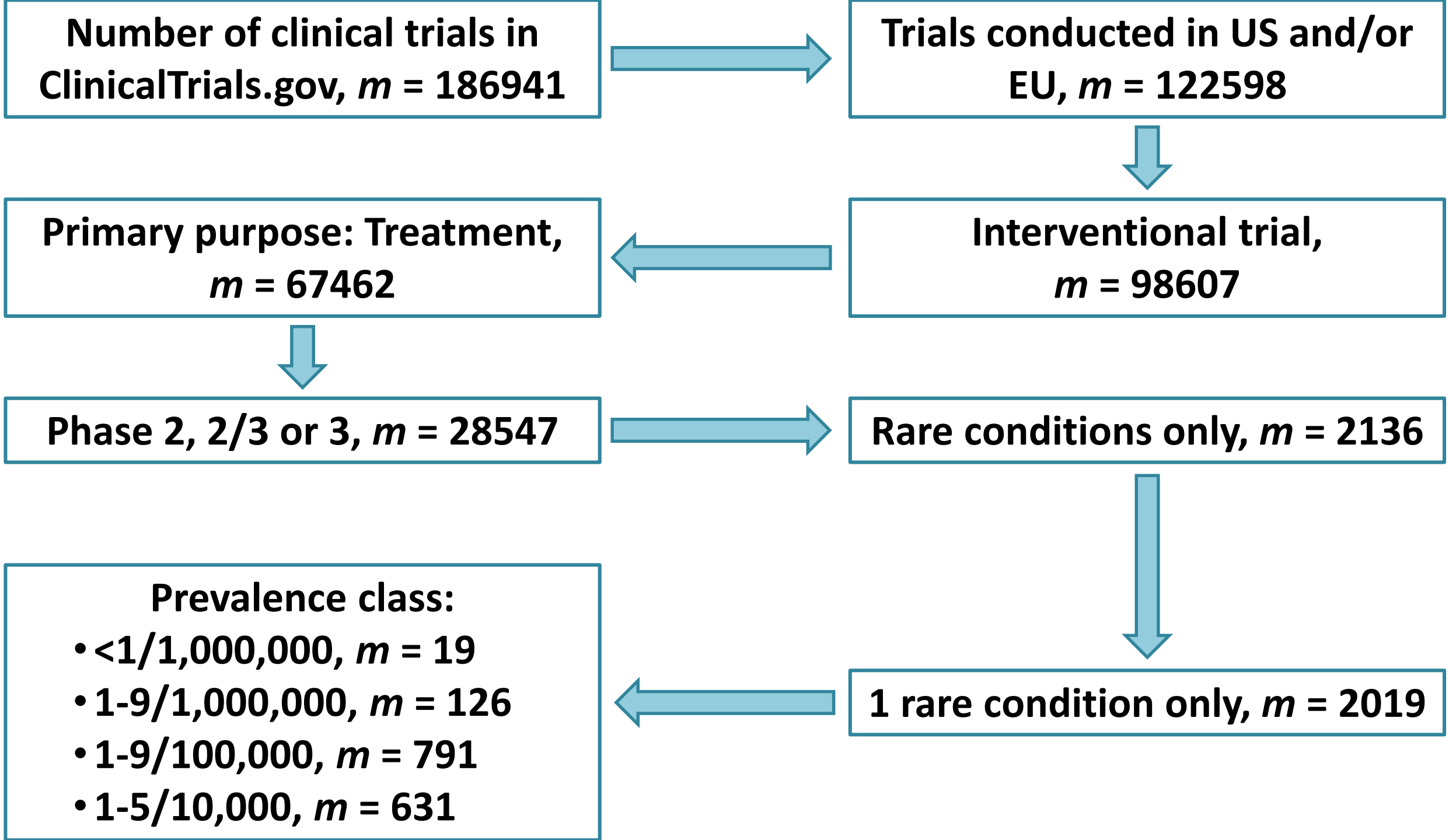
- Carglumic acid for hyperammonaemia due to N-acetyl glutamate synthase deficiency
  - 1 pharmacokinetic study (*n* = 12 patients)
- Sorafenib tosilate for renal cell and hepatocellular carcinomas
  - 1 phase III renal trial (*n* = 903 patients)
  - 1 phase III hepatic trial (*n* = 602 patients)

Bell and Tudur Smith (*Orphanet J Rare Dis*, 2014;9(1):1-11)

	Rare disease trials	Non-rare disease trials
Anticipated enrolment, n (%)		
0-50	798 (61.7)	4556 (38.2)
51-100	280 (21.6)	2731 (22.9)
101-500	195 (15.1)	3767 (31.6)
>500	21 (1.6)	877 (7.4)
Actual enrolment, n (%)		
0-50	955 (71.4)	3570 (43.3)
51-100	211 (15.8)	1607 (19.5)
101-500	158 (11.8)	2402 (29.1)
>500	14 (1.0)	672 (8.1)

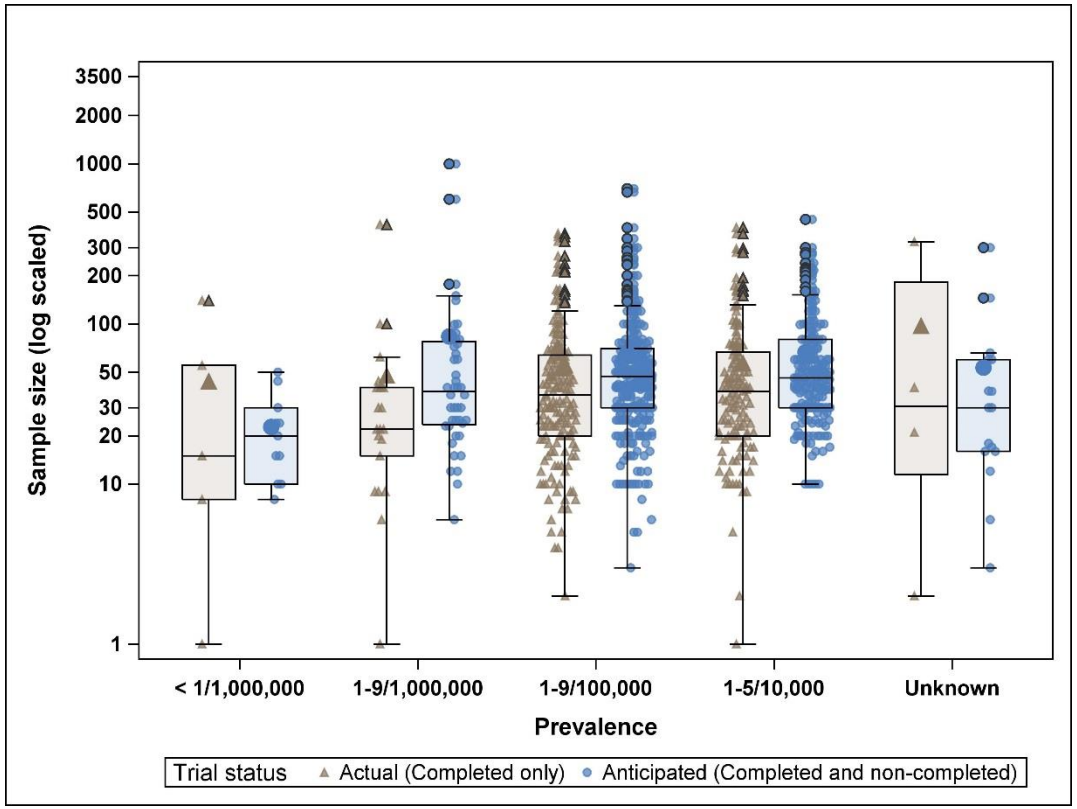
Hee *et al.* (*Oprhanet J Rare Dis*, 2017;12:44)

- Association between disease prevalence and sample size for rare disease clinical trials
- ClinicalTrials.gov database (Aggregate Analysis of ClinicalTrials.gov, AACT)
- Orphadata, a database of rare diseases compiled by Orphanet

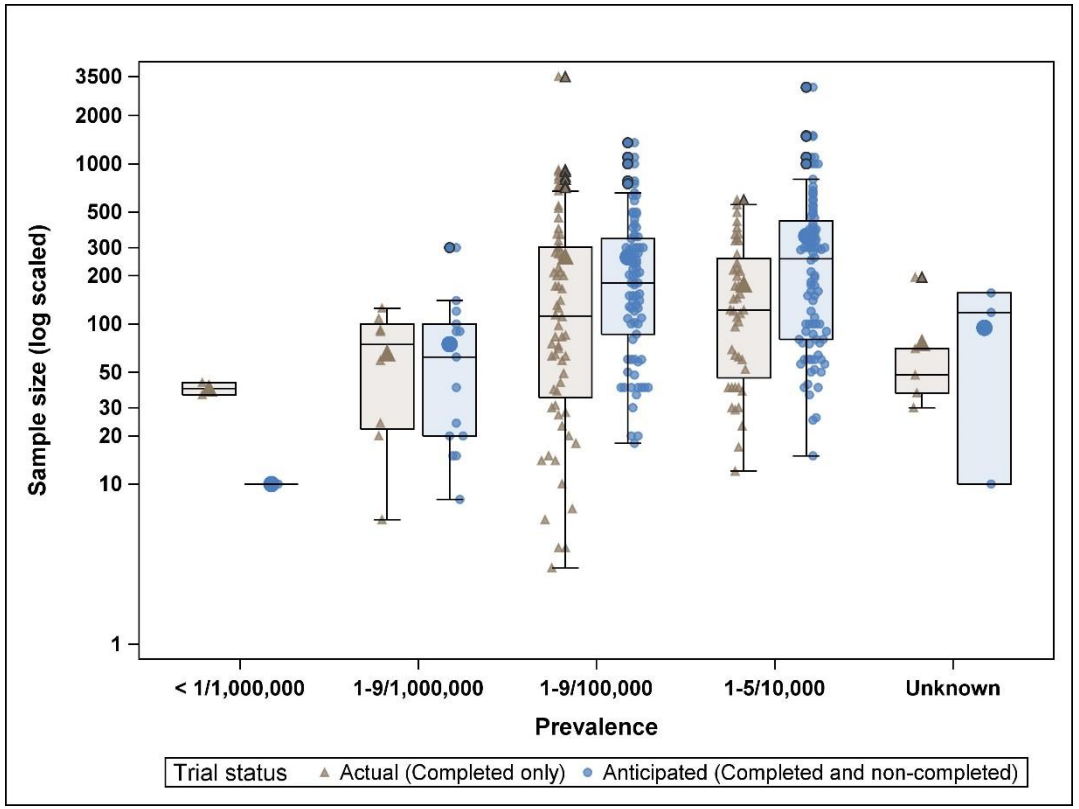

Number of clinical trials in ClinicalTrials.gov, m = 186941
Trials conducted in US and/or EU, m = 122598
Interventional trial, m = 98607
Primary purpose: Treatment, m = 67462
Phase 2, 2/3 or 3, m = 28547
Rare conditions only, m = 2136
1 rare condition only, m = 2019
Prevalence class:
• <1/1,000,000, m = 19
• 1-9/1,000,000, m = 126
• 1-9/100,000, m = 791
• 1-5/10,000, m = 631

Results

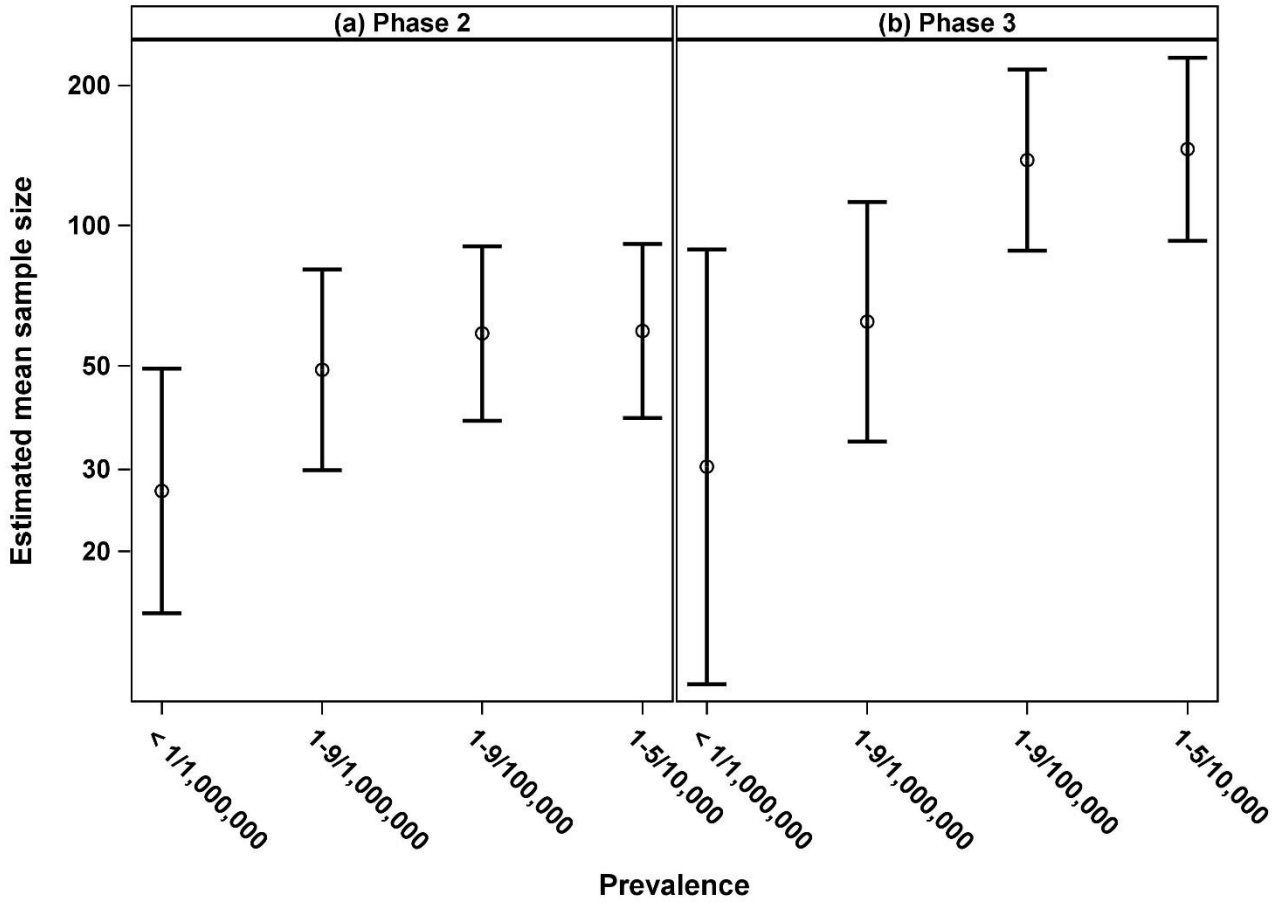
Phase II



Phase II/III



Fitted mean by prevalence and phase*



* adjusting for gender, age, whether or not the trial had a DMC, whether or not the intervention was FDA regulated, intervention model, trial regions, number of countries participating in the trial, year that enrolment to the protocol begins and number of arms

Alternative to frequentist

- The outcome is relatively simple, e.g. “Go/No-Go”
- Bayesian decision-theoretic approach
- An optimal decision is made between a number of possible actions on the basis of the consequences of each action under all possible scenarios

Notation

- Responses, $Y = (y_1, y_2, \dots, y_n)$
- Unknown parameter, θ
- Set of possible actions, $\mathcal{A} = \{a_1, a_2, \dots\}$
- Utility function for action a, $U_a(\theta)$

$$\underset{n}{\operatorname{argmax}} \left\{ \int \max_{a} \left\{ \int U_a(\theta) p(\theta|y,n) d\theta \right\} f(y|n) dy \right\}$$

Methodological design

Types of design		Simple utility				More realistic utility			
		Patient	Regulatory / societal	Commercial	Not specified	Patient	Regulatory / societal	Commercial	Not specified
Single stage	Single-arm				4				1
	Two-arm			1		3	13	13	
Multi-stage	Single-arm				5			6	1
	Two-arm	1			13		1	3	1
Multi-arm				2	3			2	
Enrichment									1
Series of trials			1	2				4	

The total number of articles in the cells exceed 67 as some described more than one design or perspective.

Hee *et al.* (*Stat Methods Med Res*, 2016;25(3):1022-1038)

Decision-theoretic design

- Specification of a prior distribution
  - Commonly: beta, normal
- Constructing utility function
  - Reflect the preferences of consequences from the point of view of the decision maker

Decision-theoretic design with value of information (VoI)

- Decision-maker: society
- Costs: making type I error, treating patients, conducting the trial
- Gain: profit from successful treatment, potential gain to future patients
- Actions: approve the experimental treatment ($\bar{y} > \frac{z_\alpha \tau}{\sqrt{n}}$), do not approve

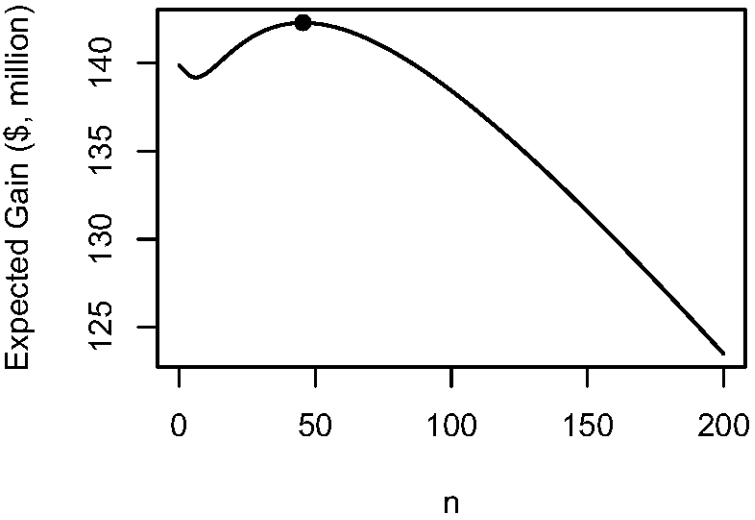
Pearce *et al.* Value of information methods to design a clinical trial in a small population to optimise a health economic utility function. *In preparation*.

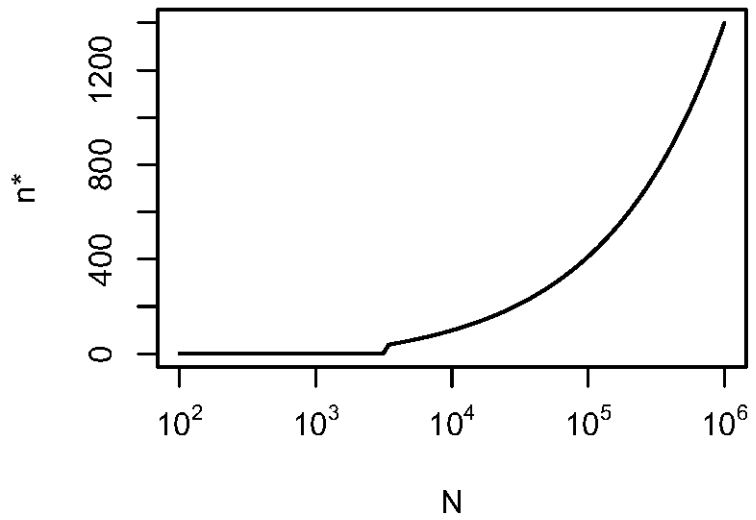
Example: trial in haemophilia A

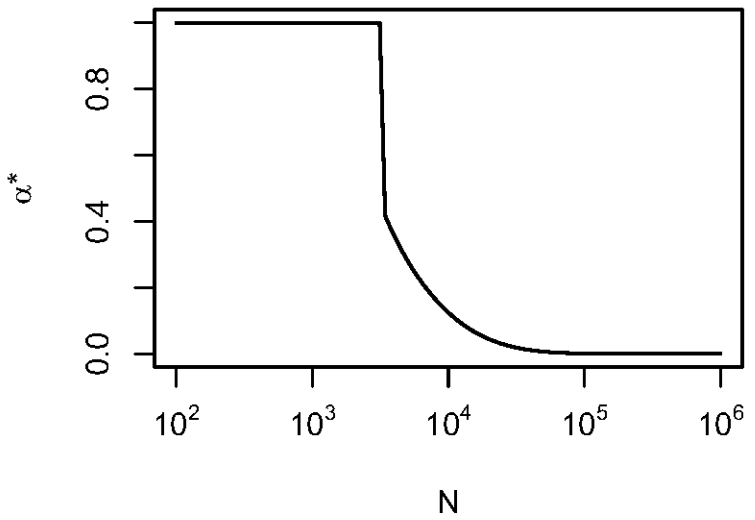
- Cost: $1m (trial), $5000 (patient)
- Treatment cost: $61,032 (patient)
- Population: 4000 (20 years)
  - Incidence: 200 but only 1/5 will be in the trial

Abrahamyan *et al.* (*J Gen Intern Med*, 2014;29(3): 767–773)

Results



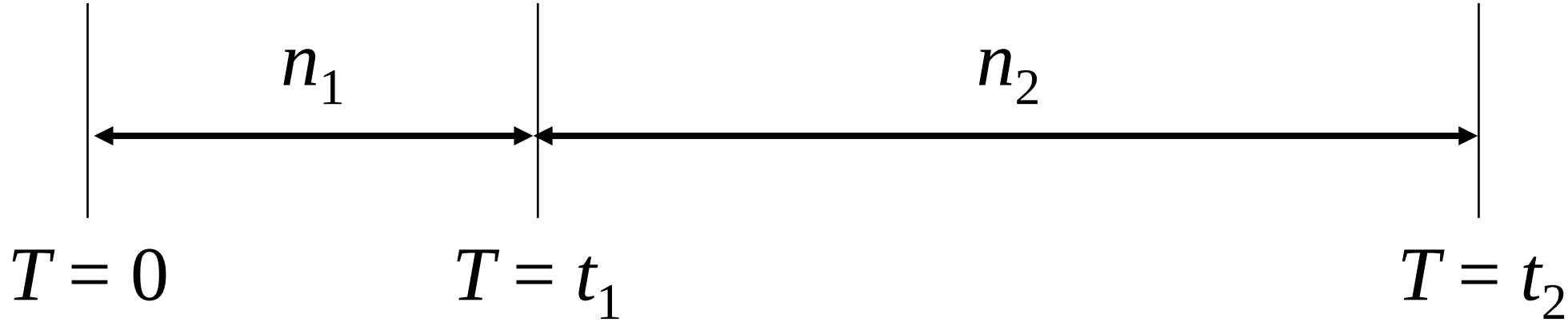




n^* = 46 (23 per arm)

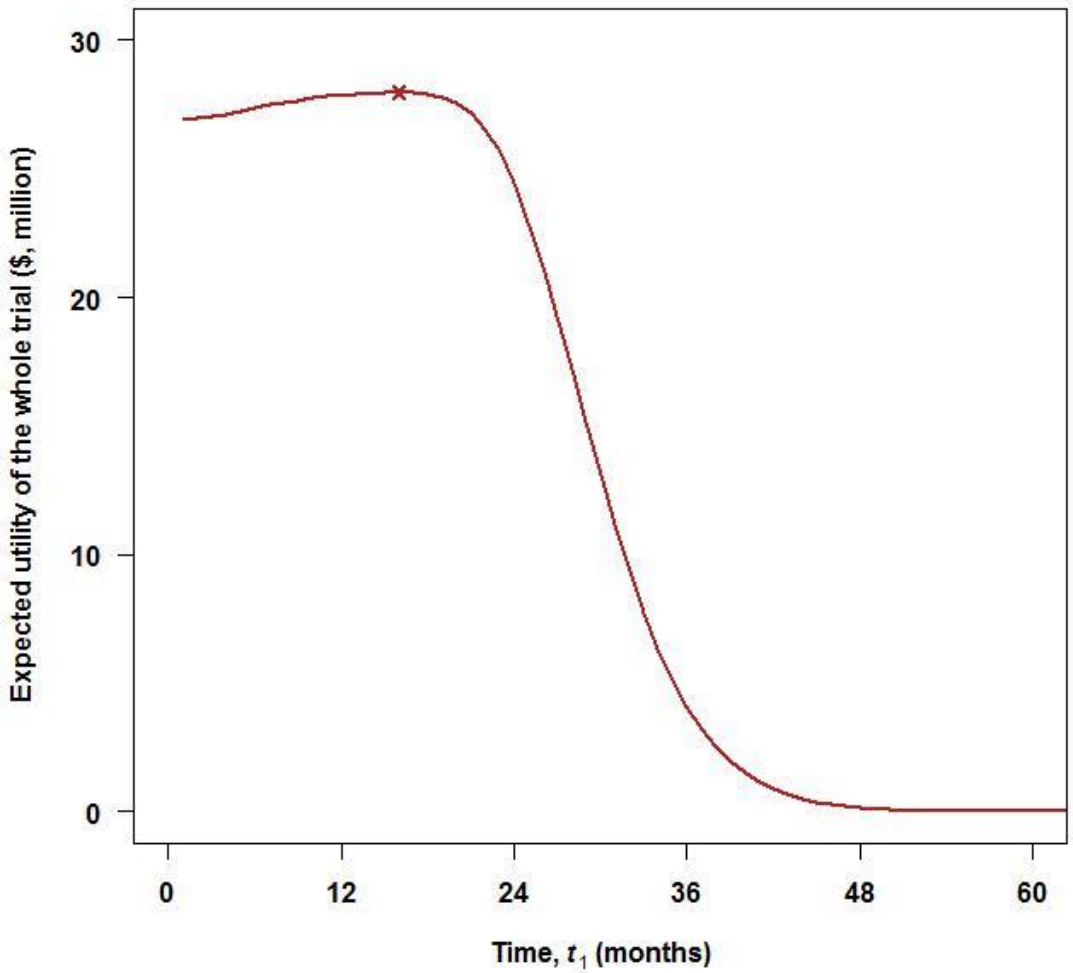
α^* = 0.35615

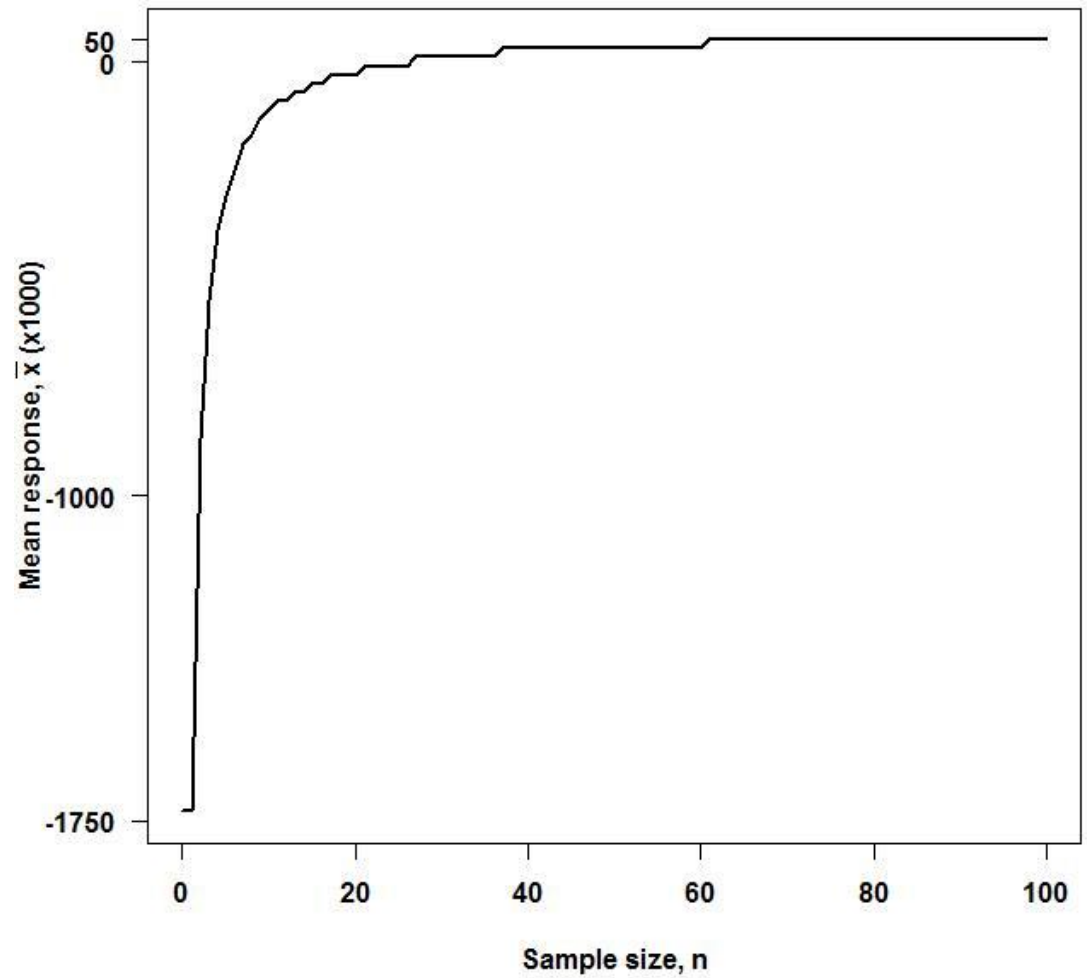
Random population size



- $N \sim \text{Poisson}(\lambda)$
- $\lambda \sim \text{Gamma}(a, b)$
- $Y \sim \text{Normal}(\theta, \tau^2/n)$
- $\theta \sim \text{Normal}(\mu, \sigma^2)$

Result: t^* = 16 months





The last leg

- Multi-stage
- Unknown variance