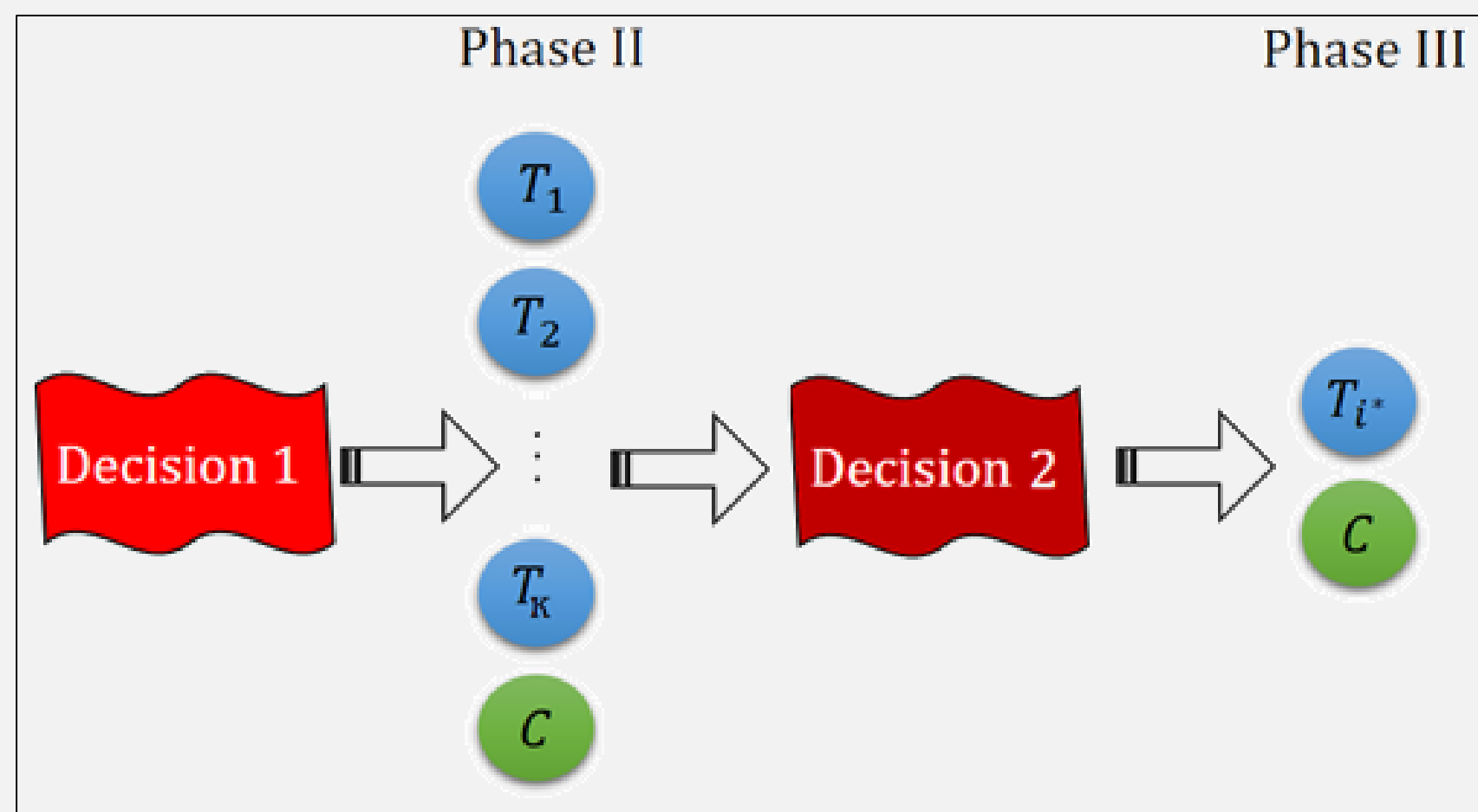




Studying Phase II and III as a programme

- Previous research focusses on *individual phases* of Phase II (*treatment selection*) and Phase III (*confirmatory evidence of efficacy*). Relatively less treats Phase II and III as a *programme*.



Bayesian Decision Theory

- *Bayes' decision rule* provides 'optimal' decisions.
- Decisions made maximise the *expected value* of some *Gain Function* given information observed so far.
- Decisions include
 - *samples sizes* of Phase II, III, and
 - *which treatment/dose* to use.

A 'Net Present Value' Gain Function

$$\text{Gain} := \text{Discounted Revenue (DR)} - \text{PhII Cost} - \text{PhIII Cost}$$

$$\text{DR} := \int_{T_{\text{PhII}} + T_{\text{PhIII}}}^{\infty} g(t, T_{\text{pat}}) e^{-\rho t} dt \times \zeta(\theta) 1_{(H_0 \text{ rejected})}, \quad \text{where}$$

$$g(t, T_{\text{pat}}) := \begin{cases} G & \text{if } t \leq T_{\text{pat}} \\ G e^{-c(t - T_{\text{pat}})} & \text{if } t \geq T_{\text{pat}} \end{cases}$$

$$\text{PhII Cost} := \gamma_1 K n_1 + \gamma_{\text{overhead}} T_{\text{PhII}}$$

$$T_{\text{PhII}} := T_{\text{PhII setup}} + T_{\text{PhII pat}} n_1$$

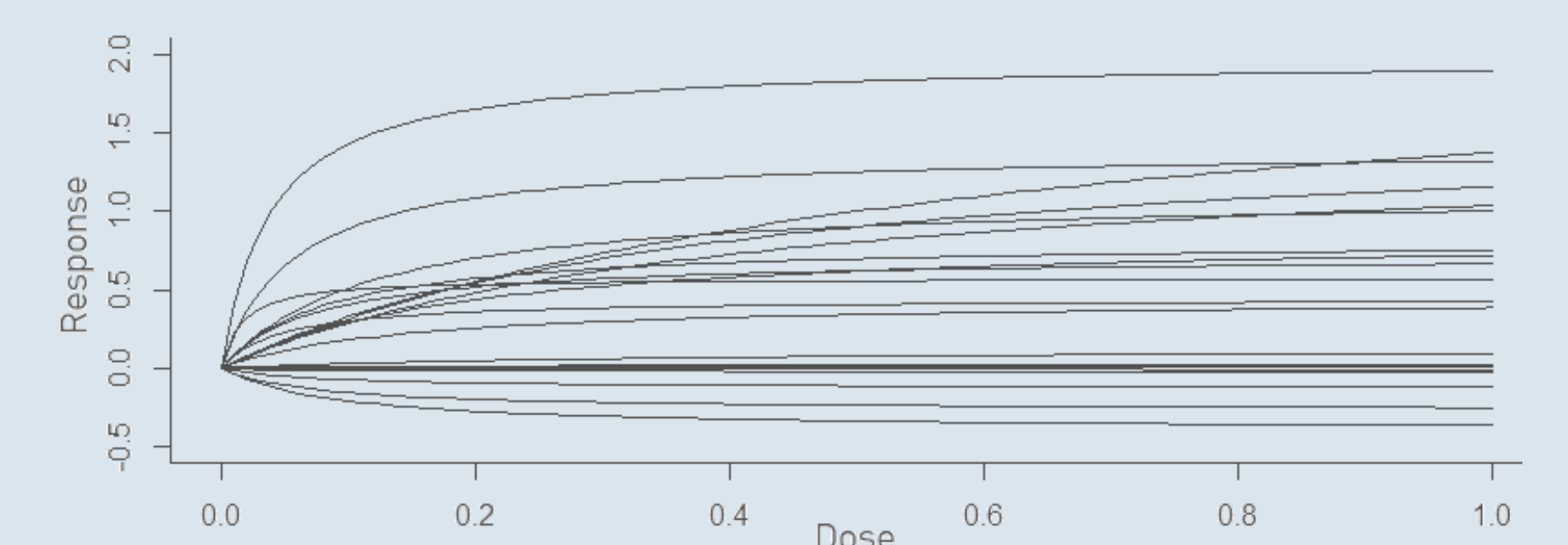
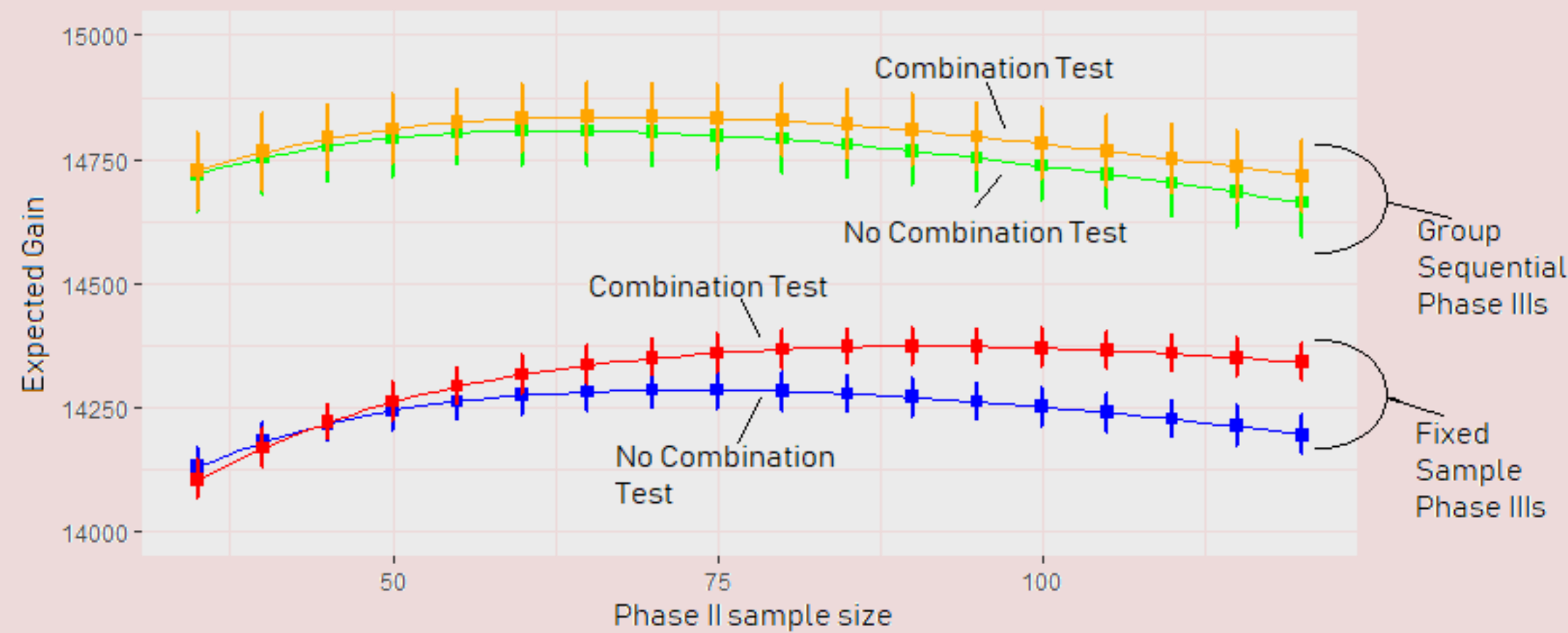
... and similarly for **PhIII Cost**.

Case Study 1: Group Sequential and Adaptive Methods

- What is the value in having
 - a *group sequential* Phase III,
 - *combination tests* to use both Phase II and III data in the hypothesis test, in the Phase II/III programme?

Results

- Both bring value, but *group sequential* methods significantly more.
- Using either changes optimal decisions in Decision 1 and 2.



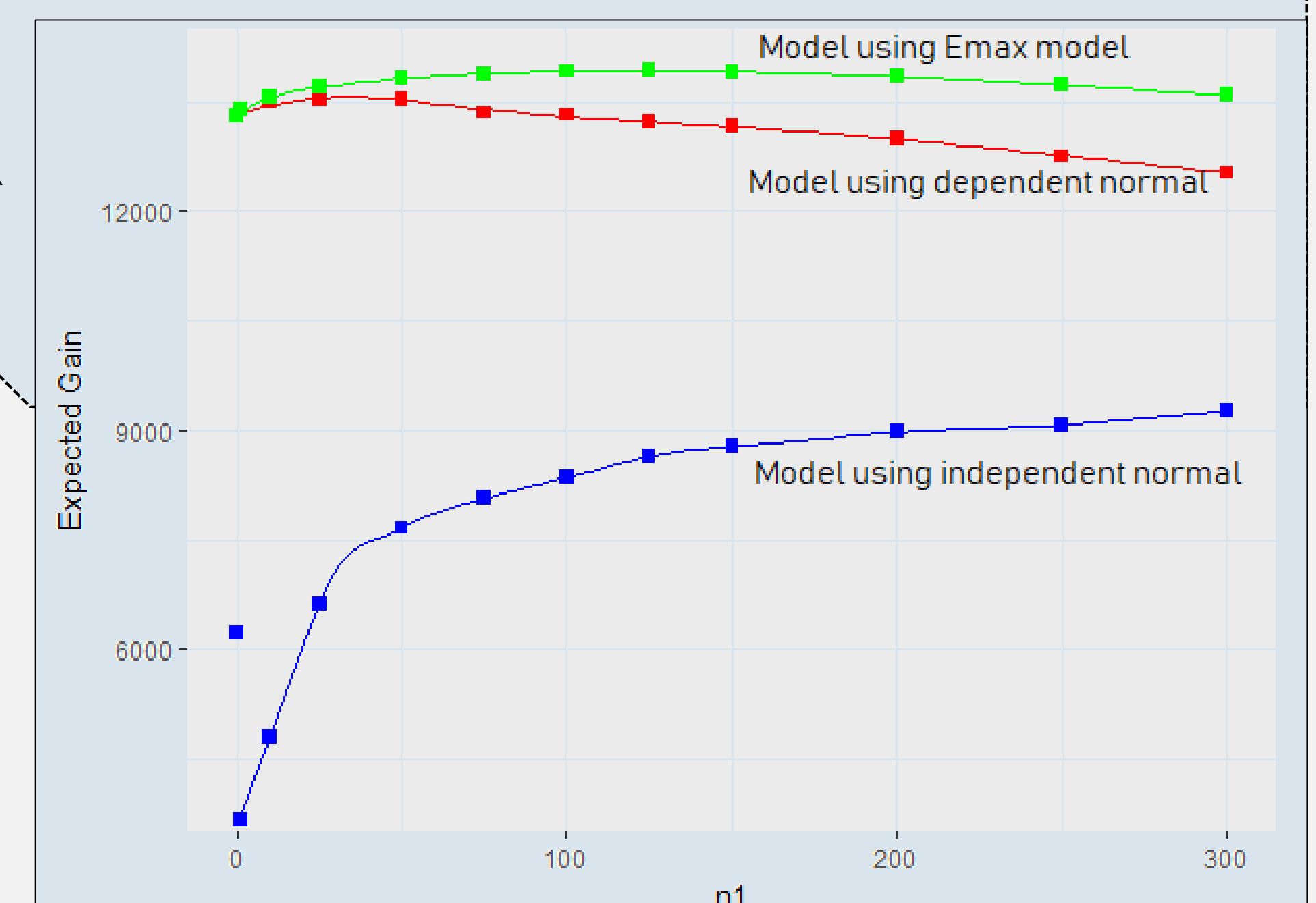
Case Study 2: Dose Finding Phase II

- What is the value in using *dose response models* to learn about efficacy in phase II? What is the *loss* in value if *distributional assumptions* are made?
- When is *MCP-Mod* appropriate?

Results

Dose response data simulated from an *Emax* model. Data was modelled using (i) **independent** and (ii) **dependent** MVN random variables and (iii) an **Emax model**. Compare relative gain of each approach.

- Only the correct **Emax model** obtains full use of data from Phase II to make fully optimal decisions.
- **Dependent MVN** is a good approximation.
- **Independent MVN** significantly *harms* the programme by making bad decisions.

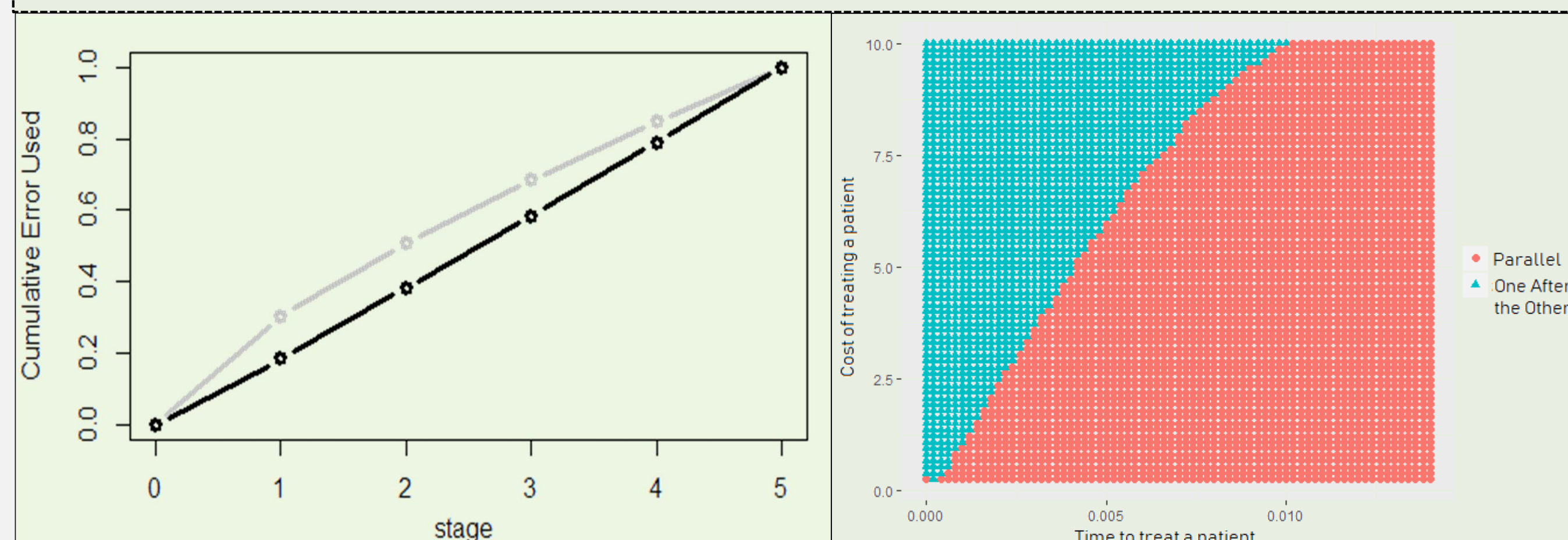


Case Study 3: 2 Phase IIIs

- If two Phase III trials are performed, should they be done in *parallel* or *one after each other*? Is there justification for *waiting* until halfway through the first Phase III trial before starting the next?
- What are the *optimal group sequential boundaries* for 2 Phase III trials?

Results

- In most realistic circumstances, it is better to perform them in *parallel*.
- Optimal boundaries for 2 Phase IIIs 'spend more error' *later* than optimal boundaries for 1 Phase III.



Computations to Find Bayes' Optimal Decision Rules

- Search over samples sizes and treatments to take forward.
- Each time, need to calculate *expected gain conditional on data observed so far*.
- *Numerical Integration Approach*: Later decisions when integral is only single or double.
- *Monte carlo Approach*: When multiple treatments (and integrals) in Decision 1 (incorporate splines, coupling, and is easily parallelised).