

Project specification challenge:
Optimising the design of successive
Phase IIb and Phase III trials

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The Phase IIb / Phase III problem

Your company has decided to review the way that resources are allocated to Phase IIb (dose finding) and Phase III (confirmatory) trials

Your team is asked to develop software to carry out joint optimisation of Phase IIb and Phase III trial designs.

Today's task is for you to develop the specification for this project, following the guidance of the "Best practice" document.

A Company Working Group has identified the main elements to be included in the modelling and optimisation process.

I shall describe these elements to you and give you chance to ask for clarification on what your software should be able to do.

Model ingredients and the optimisation task

1. Modelling the Phase IIb and Phase III trials

Dose response model and prior for Bayesian analysis

Phase IIb and Phase III trial designs (to be scaled by sample size)

Phase IIb responses, Phase III responses and the final decision

Gain function and sampling costs

Risk of losing the drug altogether due to poor safety results

2. Decisions to be made in optimising Phase IIb / Phase III:

Phase IIb sample size,

“Go/no go” to Phase III,

Selecting the dose to test vs control in Phase III,

Phase III sample size

3. Formulate the above as a Bayes sequential decision problem and solve this!

Model ingredients and the optimisation task

In reality, you would need to determine model assumptions, etc., in discussions with the Company Working Group and possibly other interested parties.

In order to get started quickly, I shall assume some of these discussions have taken place and present the resulting information.

You will have chance to ask for further information before you get down to work on your project specification.

The optimisation task is challenging

I shall outline an approach that I have implemented on similar problems.

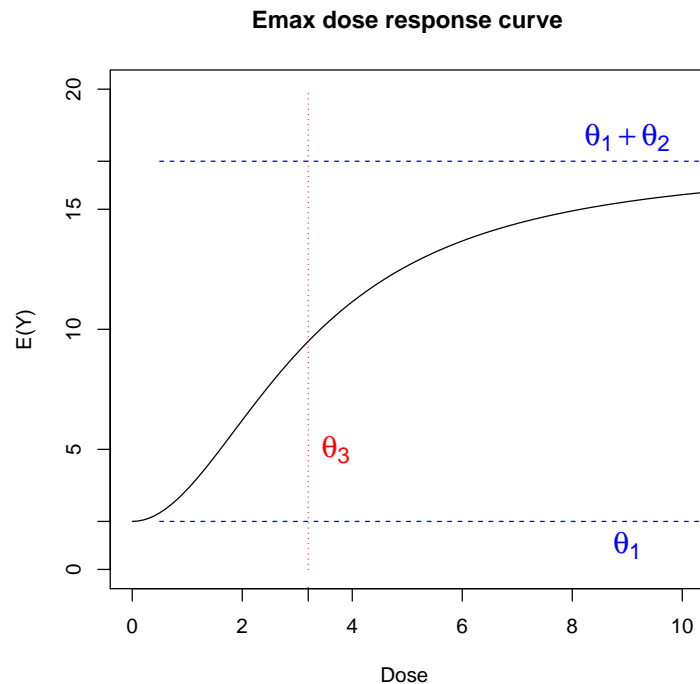
I shall the show some results to illustrate what your software could produce.

The Emax dose response model

We shall assume a 4 parameter Emax dose-response model.

In this model, the mean response at dose d is

$$\mu(d) = \theta_1 + \theta_2 \frac{d^{\theta_4}}{\theta_3^{\theta_4} + d^{\theta_4}}.$$



θ_1 : Mean response at dose zero
(placebo effect)

θ_2 : Increase in mean response from
dose zero to a very high dose

θ_3 : ED50, the dose achieving half
this maximum increase

θ_4 : Governs the steepness of the
dose response curve

The Emax dose response model

Suppose we investigate n active doses and the control.

The control has a “dose” $d_0 = 0$.

The active doses are $d_j, j = 1, \dots, n$.

The Emax model gives mean responses

$$\mu_j = \theta_1 + \theta_2 \frac{d_j^{\theta_4}}{\theta_3^{\theta_4} + d_j^{\theta_4}}, \quad j = 0, \dots, n.$$

For a patient receiving dose d_j , we observe a response

$$X \sim N(\mu_j, \sigma^2)$$

as the primary endpoint.

The prior distribution for the Emax model parameters

The prior will play a crucial role in the Bayesian analysis.

When a new treatment approaches the Phase IIb stage, a suitable prior should be elicited from expert opinions, drawing on relevant previous experience.

Suppose 7 doses, $d_1 = 1, \dots, d_7 = 7$, (in certain units) are to be considered.

We might assume a prior distribution in which the four Emax model parameters are independent with

$$\theta_1 \sim N(5, 10^2),$$

$$\theta_2 \sim N(5, 10^2),$$

$$\theta_3 \sim N^+(3.5, 7^2),$$

$$\theta_4 \sim N^+(1, 1).$$

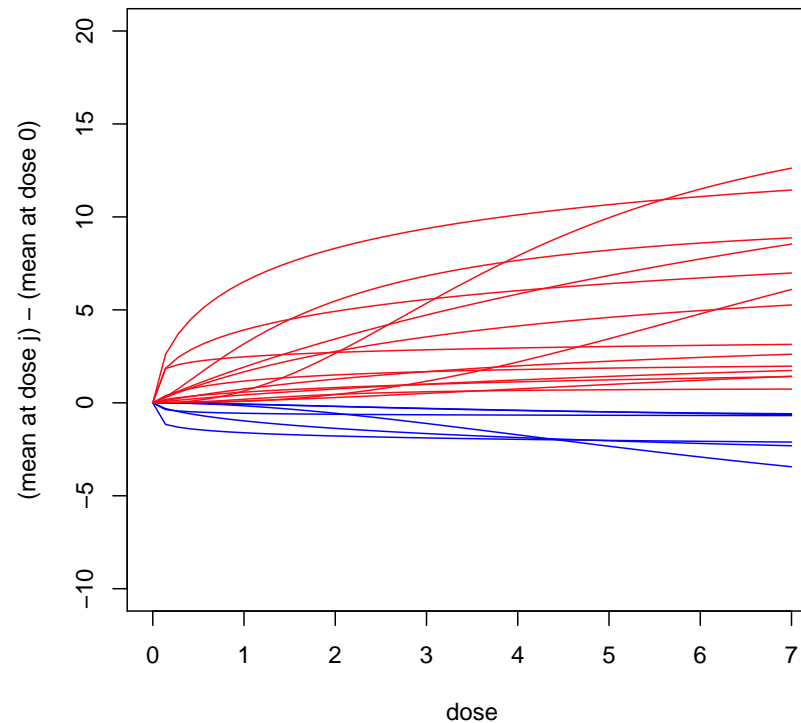
Here, N^+ denotes a normal distribution restricted to positive values.

Assessing the prior for Emax model parameters

The following plot shows a sample of 20 Emax dose response curves using parameter values generated from the prior on the previous slide.

Note that the plot is of the increase in mean response over dose zero.

The curves with a negative treatment effect are coloured blue.



Phase IIb and Phase III trials

Suppose the same endpoint will be observed in the Phase IIb and Phase III trials.

Given Emax model parameters $(\theta_1, \theta_2, \theta_3, \theta_4)$, we assume subjects on dose d_j have independent, normally distributed responses

$$X_{ij} \sim N(\mu_j, \sigma^2),$$

where μ_j is given by the Emax model formula.

In Phase IIb, a total of n_2 patients are to be recruited.

These patients will be randomised to each active dose and the control (dose zero).

After Phase IIb, investigators must decide whether or not to continue to Phase III.

If so, they must select

- (i) the dose to study in Phase III,
- (ii) the sample size to be used in the two Phase III trials.

The Phase III trials

Suppose it is decided to test dose d_j against control in Phase III.

We run two Phase III trials.

In each, $2n_3$ subjects are randomised equally between dose 0 and dose d_j .

Responses are distributed as

$$X_{i0} \sim N(\mu_0, \sigma^2) \quad \text{on dose zero,}$$

$$X_{ij} \sim N(\mu_j, \sigma^2) \quad \text{on dose } d_j.$$

In each trial, we test $H_{0j}: \mu_j - \mu_0 \leq 0$ against $\mu_j - \mu_0 > 0$.

If H_{0j} is rejected at a (one-sided) significance level below $\alpha = 0.025$ in both trials, efficacy of dose d_j is established.

Gain function and sampling costs

We suppose a positive outcome in Phase III leads to approval of the new drug and a financial gain g .

Running the Phase IIb trial incurs a sampling cost of c_2 per subject.

Running the Phase III trial incurs a cost of c_3 per subject.

The costs c_2 and c_3 can be as high as £20,000 or £30,000, depending on the condition being investigated .

Authors writing on this topic have used values of the order of $g = 10,000 c_3$ to $g = 15,000 c_3$, representing a multi-million pound return on a successful new treatment.

Risk of failure for safety

Suppose the probability that dose d will eventually fail on safety grounds is $\gamma(d)$.

This could occur in Phase III or later on in post-marketing surveillance.

We shall assume $\gamma(d)$ is a known, increasing function of d .

The function $\gamma(d)$ is specified before Phase IIb; we assume follow-up in Phase IIb will not be long enough to learn more about the safety profile.

As an example, with doses $d_1 = 1, \dots, d_7 = 7$, we might suppose $\gamma(d)$ to be quadratic with $\gamma(7) = 0.2$.

Thus, the risk for dose j is

$$\gamma_j = (j/7)^2 \times 0.2.$$

When Phase III has a positive outcome, we calculate the expected gain by discounting the gain function by a factor $1 - \gamma_j$.

Optimising the Phase IIb / Phase III design

Before Phase IIb

We choose the Phase IIb sample size, n_2 .

At the end of Phase IIb

We decide whether to proceed to run Phase III and, if so, select

The dose to test in Phase III d_j ,

The Phase III sample size n_3 .

We wish to optimise:

The choice of n_2 ,

The rule for deciding whether to proceed to Phase III,

The rule for choosing d_j and n_3 .

Optimisation algorithm

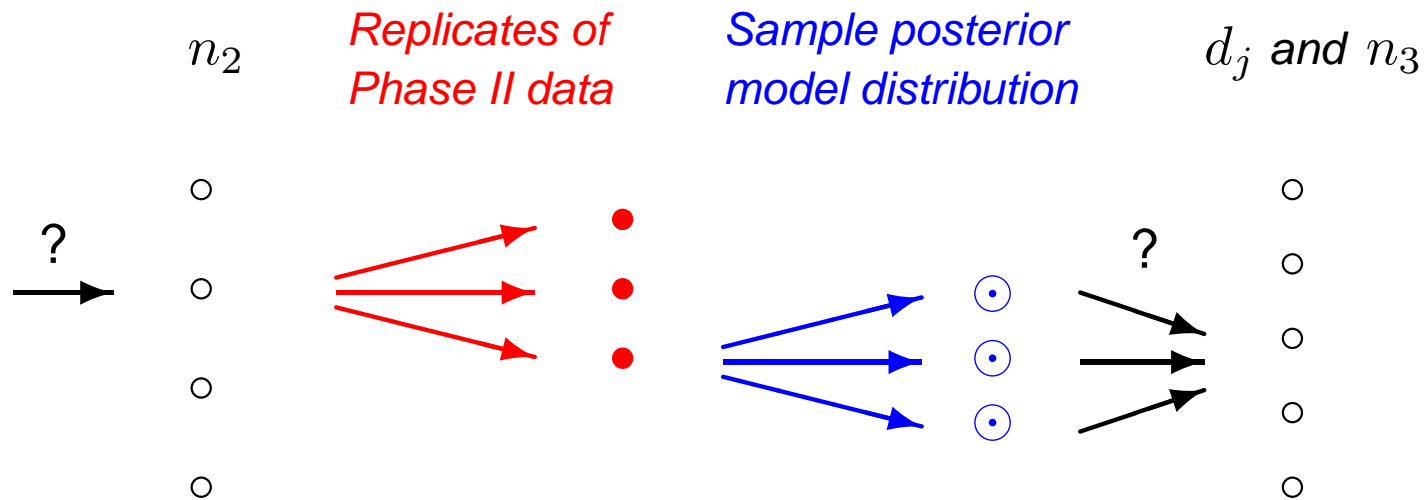
For a particular n_2 :

Simulate θ , the vector of dose response curve parameters, from the prior.

Simulate Phase IIb data, given θ .

Evaluate Phase III options given the posterior for θ and choose the best option after observing these Phase IIb data.

Average over replicates to compute the expected net gain for this n_2 .



Compare $E(\text{Net gain})$ over possible choices of n_2 and choose the best n_2 .

Evaluating Phase III options

If we decide to run Phase III trials with dose d_j and sample size n_3 , the conditional expectation of the net gain, given Phase IIb data $X = x$, is

$$\int [P_{\theta}\{\text{Positive Phase III}; d_j, n_3\} (1 - \gamma_j) g - 4 n_3 c_3 - n_2 c_2] \pi_{\theta|X}(\theta|x) d\theta,$$

where $\pi_{\theta|X}(\theta|x)$ denotes the posterior density of θ given $X = x$.

We estimate this conditional expected net gain by

$$\frac{1}{S} \sum_{s=1}^S P_{\theta^s}\{\text{Positive Phase III}; d_j, n_3\} (1 - \gamma_j) g - 4 n_3 c_3 - n_2 c_2, \quad (1)$$

where θ^s , $s = 1, \dots, S$, is a sample from $\pi_{\theta|X}(\theta|x)$.

The optimal Phase III design is that which maximises (1) over d_j and n_3 .

Any questions?

At this point you should break off into teams and spend 5 or 10 minutes thinking of any questions that you would like to ask before embarking on the project specification.

These can be questions that you would like to ask the Company Working Group or other experts in (or outside) the company.

We shall have a short session where I provide answers to these questions.

I can also show you some results from one particular example to illustrate what your software should be able to do.

Results for a simple example

Consider a problem with 7 active dose levels $d_j = j, j = 1, \dots, 7$.

Following the earlier definition, the prior distribution for $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$ has

$$\begin{aligned}\theta_1 &\sim N(5, 10^2), & \theta_2 &\sim N(5, 10^2), \\ \theta_3 &\sim N^+(3.5, 7^2), & \theta_4 &\sim N^+(1, 1).\end{aligned}$$

Phase IIb has $0.3 n_2$ subjects on dose zero and $0.1 n_2$ on each active dose.

The sampling cost is 1 unit for each Phase IIb and Phase III subject.

The financial gain for a positive Phase III trial is $g = 12,000$.

But dose d_j may fail on safety grounds with probability

$$\begin{aligned}\gamma_1 &= 0.004, & \gamma_2 &= 0.016, & \gamma_3 &= 0.037, & \gamma_4 &= 0.065, \\ \gamma_5 &= 0.10, & \gamma_6 &= 0.15, & \gamma_7 &= 0.2.\end{aligned}$$

Results for a simple example

We have optimised over Phase III sample sizes

$$n_3 \in \{50, 75, 100, 125, 150, 200, 250, 300, 400, 500\}.$$

Comparing Phase IIb designs, we find:

n_2	$E(\text{Net gain})$	n_2	$E(\text{Net gain})$
25	4,375	200	4,630
50	4,450	250	4,635
75	4,520	300	4,650
100	4,555	350	4,645
125	4,575	400	4,645
150	4,600	450	4,630
175	4,615	500	4,605

So, we conclude the optimal choice is $n_2 = 300$.

Breakdown of the expected net gain

The $E(\text{Net gain})$ values are made up from:

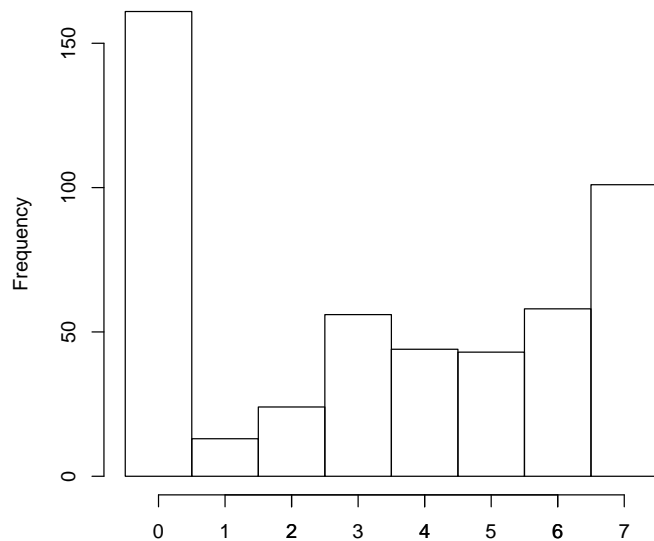
n_2	$P(\text{Overall success}^*)$	$4 E(N_3)$	$E(\text{Net gain})$
25	0.441	893	4,375
50	0.447	861	4,450
100	0.460	862	4,555
150	0.466	837	4,600
200	0.473	843	4,630
250	0.478	854	4,635
300	0.483	850	4,650
350	0.487	847	4,645
400	0.490	840	4,645
450	0.492	823	4,630
500	0.493	814	4,605

* Two successful Phase III trials and no safety problems.

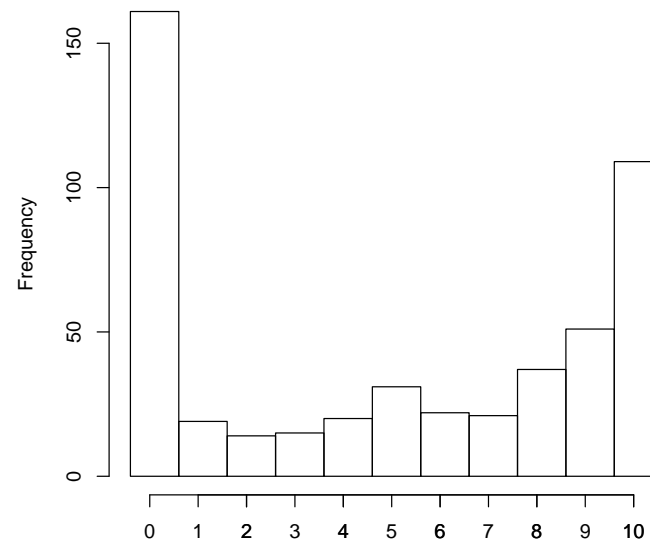
Results for a simple example

Within replicates of Phase IIb data for $n_2 = 300$, the optimal choice of d_j and n_3 varies considerably:

Optimal Dose when using Optimal n_2



Optimal n_3 when using Optimal n_2

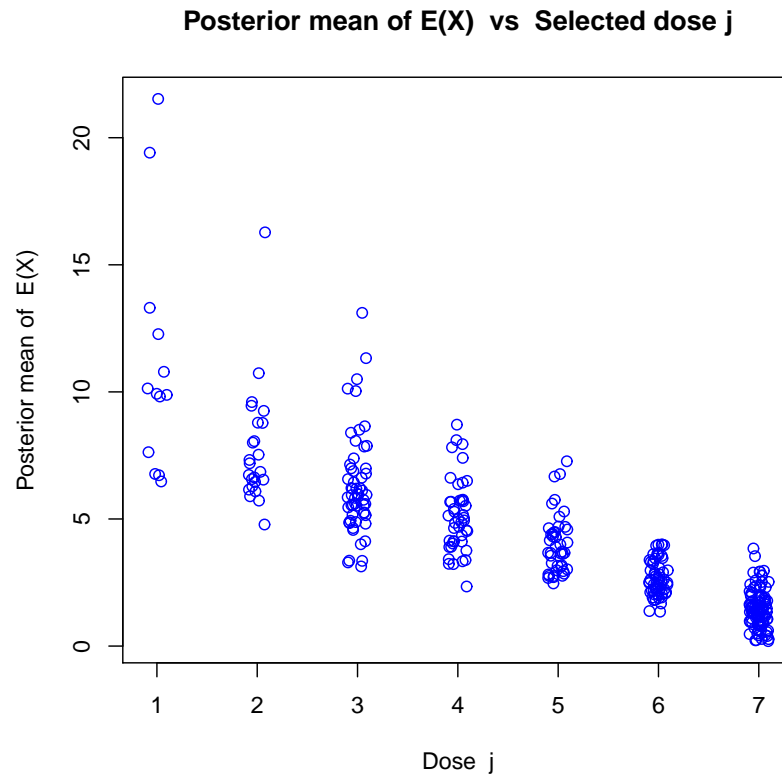


The risk of safety problems guides the decision towards lower doses.

Sampling costs in Phase III argue for lower values of n_3 .

Results for a simple example

We can explore the decisions made in selecting a dose to go forward to Phase III.



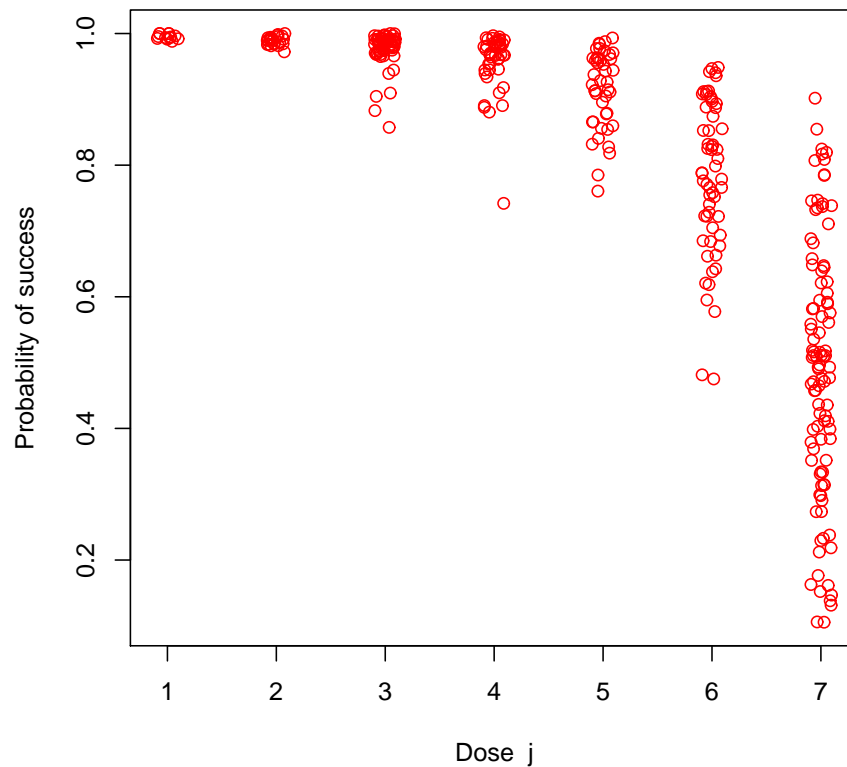
A high dose is selected when the posterior samples of the dose response curve show modest treatment effects.

More promising results lead to lower doses being chosen (especially for higher n_2).

Results for a simple example

High posterior means for $E(X)$ translate into high Phase III success probabilities.

Probability of success in Phase III vs Selected dose j



For the highest doses, probability of Phase III success is offset by greater risk of safety problems.

Extending the methodology

Phase III options

Group sequential Phase III designs.

Allowing two or more active doses to be tested in Phase III.

Gain function and costs

Define the gain function to be the net present value based on:

patent life remaining after a successful Phase III,

true treatment effect (or estimated effect?) at selected dose.

Elicit a problem-specific gain function for two successful doses in Phase III.

Portfolio management: Choosing which of several candidate treatments (possibly for different indications) should go forward to a Phase III trial.

Extending the methodology

Additional model features

Learning about safety problems in Phase IIb.

Change of endpoint between Phase IIb and Phase III.

Phase IIb options

Different fixed patterns of dose allocation.

Adaptive dose-allocation.

Early stopping in Phase IIb.