

# ***Optimising the Phase IIb / Phase III Process***

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## Outline of talk

### 1. Elements of the Phase IIb / Phase III decision process

Dose response model and prior for Bayesian analysis

Phase IIb responses, Phase III responses and the final decision

Gain function and sampling costs

Risk of losing a drug due to poor safety results

### 2. Optimising Phase IIb / Phase III

Formulation of the problem

An optimisation algorithm

Some preliminary results

### 3. Extensions and methods for improving computational speed

## Dose response model and prior for Bayesian analysis

Doses  $d_0 = 0$  (control) and  $d_j, j = 1, \dots, J$ , (active) are to be tested.

We assume a 4 parameter logistic model with mean response at dose  $d_j$

$$\mu(d_j) = \beta + \frac{\delta}{1 + \exp\{(\theta - d_j)/\tau\}}.$$

In the prior, we suppose the four parameters are independent and

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

$$\delta \sim N(15, 10^2),$$

$$\theta \sim N((d_J - d_0)/2, (d_J - d_0)^2),$$

$$\tau \sim N^+((d_J - d_0)/J, 1).$$

For  $\tau$ , we write  $N^+$  to denote a normal distribution restricted to positive values.

We shall have  $J = 7$  active doses in our example.

## Phase IIb responses

We assume a fixed Phase IIb design with  $n_{2j}$  subjects on dose  $j$ ,  $j = 0, \dots, J$ .

In our example, we suppose patients are allocated equally to each active dose and at 3 times this rate to dose zero. Thus, with a total of  $n_2$  subjects in Phase IIb,

$$n_{20} = 0.3 n_2 \quad \text{on dose zero,}$$

$$n_{2j} = (0.7/J) n_2 \quad \text{on each active dose } j = 1, \dots, J.$$

Given  $(\beta, \delta, \theta, \tau)$ , subjects on dose  $j$  have independently distributed responses

$$X_{ij} \sim N(\mu(d_j), \sigma^2).$$

We shall assume  $\sigma = 9$ .

Combining the likelihood of these responses with the prior for  $(\beta, \delta, \theta, \tau)$  gives the posterior distribution for the dose response curve to be used in designing Phase III.

## Phase III responses

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

$2n_3$  subjects are randomised equally between dose zero and dose  $d_j$ .

Responses are distributed as

$$Y_{i0} \sim N(\mu(d_0), \sigma^2) \quad \text{on dose zero,}$$

$$Y_{ij} \sim N(\mu(d_j), \sigma^2) \quad \text{on dose } j.$$

We test  $H_{0j}: \mu(d_j) - \mu(d_0) \leq 0$  against  $\mu(d_j) - \mu(d_0) > 0$ .

If  $H_{0j}$  is rejected at a significance level below  $\alpha$ , efficacy of dose  $j$  is established.

We shall use  $\alpha = 0.0005$  in our example, rather than consider two separate Phase III trials each with a target significance level of 0.025.

## 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 Phase III incurs a cost of  $c_3$  per subject.

In our example, we shall take

$$c_2 = 1,$$

$$c_3 = 1,$$

$$g = 12,000.$$

## Risk of failure for safety

We suppose there is a probability  $\gamma(d_j)$  that dose  $j$  will eventually fail on safety grounds.

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

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

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

In our example, we shall take  $\gamma(d)$  to be quadratic with  $\gamma(d_J) = 0.2$ .

Thus, when Phase III has a positive outcome, we calculate the expected gain by discounting the gain function by a factor  $1 - \gamma(d_j)$ .

## 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

### Overview

For a particular  $n_2$ ,

Simulate  $\theta$ , the vector of dose response curve parameters, from the prior.

Simulate Phase IIb data, given  $\theta$ .

Evaluate Phase III options given the posterior for  $\theta$  and choose the best option.

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

Given Phase II data  $X = x$ , denote the posterior distribution of the dose response curve parameters  $\theta$  by

$$\pi(\theta|x).$$

Consider a Phase III trial with dose  $d_j$  and sample size  $n_3$ .

The conditional expectation of the net gain is

$$\int \pi(\theta|x) [P_{\theta}\{\text{Positive Phase III}; d_j, n_3\} (1 - \gamma(d_j)) g - 2 n_3 c_3 - n_2 c_2] d\theta.$$

With a MCMC sample  $\theta^1, \dots, \theta^S$  from  $\pi(\theta|x)$ , estimate this  $E(\text{Net gain})$  by

$$\frac{1}{S} \sum_{s=1}^S P_{\theta^s}\{\text{Positive Phase III}; d_j, n_3\} (1 - \gamma(d_j)) g - 2 n_3 c_3 - n_2 c_2.$$

## 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  $\theta = (\beta, \delta, \theta, \tau)$  has

$$\beta \sim N(5, 10^2), \quad \delta \sim N(15, 10^2),$$

$$\theta \sim N(7/2, 7^2), \quad \tau \sim N^+(1, 1).$$

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 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

$$\gamma(d_1) = 0.004, \quad \gamma(d_2) = 0.016, \quad \gamma(d_3) = 0.037, \quad \gamma(d_4) = 0.065,$$

$$\gamma(d_5) = 0.10, \quad \gamma(d_6) = 0.15, \quad \gamma(d_7) = 0.2.$$

## Results for a simple example

We have optimised over Phase III sample sizes

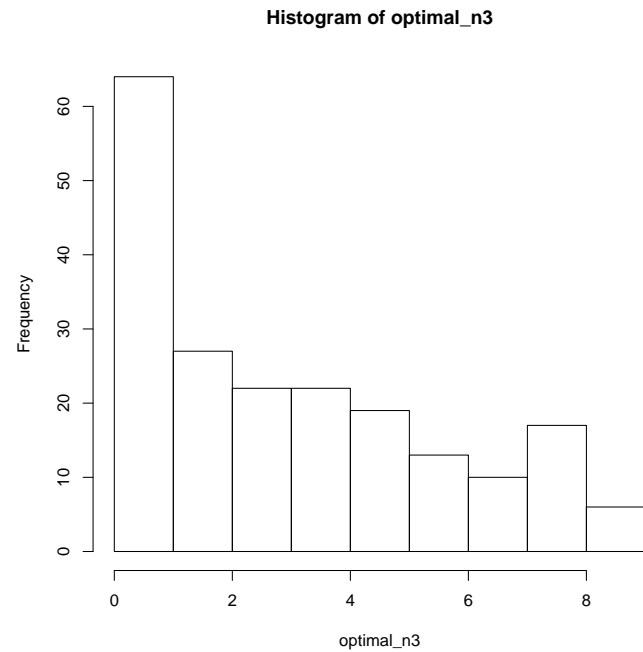
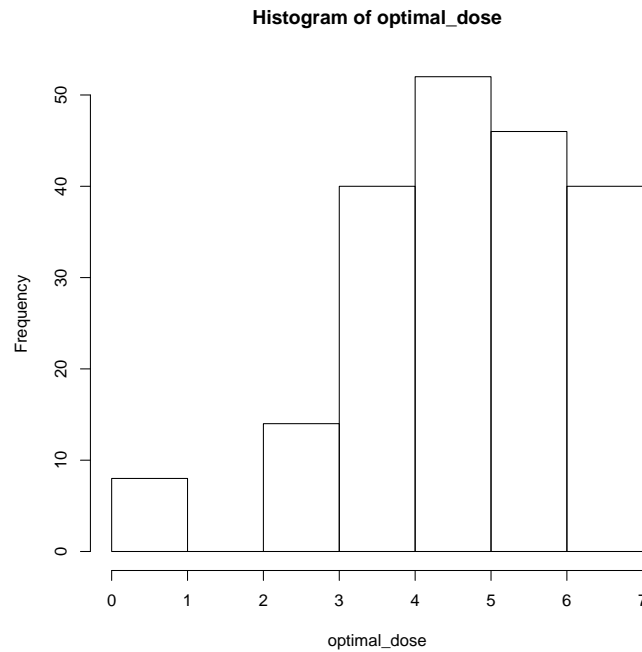
$$n_3 \in \{100, 150, 200, 250, 300, 400, 500, 600, 800, 1000\}.$$

Comparing Phase IIb designs, we found:

$n_2$	$E(\text{Net gain})$
50	8,590
100	8,760
150	8,820
<b>200</b>	<b>8,840</b>
250	8,840
300	8,820

## Results for a simple example

Within replicates of Phase IIb data for  $n_2 = 200$ , the optimal choice of  $d_j$  and  $n_3$  varies considerably:



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

The sampling cost in Phase III argues for lower values of  $n_3$ .

## 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***

Use net present value based on patent life remaining after Phase III.

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

### ***Phase IIb options***

Different fixed patterns of dose allocation.

Adaptive dose-allocation.

Early stopping in Phase IIb.

## Computational problems and possible solutions

### ***Coupling***

We have already used coupling of replicate data sets under different Phase IIb designs to increase the accuracy of comparisons *between* these designs.

### ***Multiple use of MCMC samples***

Rather than repeat MCMC simulations to sample the posterior distribution of  $\theta$  for Phase IIb data sets which are similar due to coupling, values for a “central” case can be re-used with importance sampling weights to provide results for other cases.

### ***Pre-computing for a reference set of cases***

Evaluation of more complex Phase III designs (group sequential or multi-armed) is computationally demanding. These can be evaluated up-front on a grid of parameter values, to provide a look-up table for cases arising in simulations.

## Conclusions

A full treatment of the Phase IIb/ Phase III design process is possible, with joint optimisation of both stages under a Bayesian model.

The Bayesian approach allows propagation of uncertainty and provides a natural framework for decision making under uncertainty.

MCMC simulations nested within replicates of Phase IIb data constitute a substantial computation task: but there are several routes to recovering computational efficiency and making this task feasible.

Rules for dose selection and Phase II design are often based on point estimates of the treatment effects at individual doses. Comparison with optimised decision rules will provide a check on such rules and insight into their strengths and weaknesses.

Rules can be assessed under a random distribution of  $\theta$  values from the prior or under a specific  $\theta$  (but optimisation is still based on the assumed prior for  $\theta$ ).