Jointly optimal design of Phase II and Phase III clinical trials: an over-arching approach

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The Phase II / Phase III problem

*Phases of drug development occur sequentially.*

There has been a lot of work on “optimising” phases individually — but not much on designing the overall development process.

*Dose finding in Phase IIb is often based on a non-linear, parametric dose response model with 3 or 4 parameters.*

We shall need to estimate these parameters after Phase IIb and make decisions for Phase III design based on these estimates.

In a Bayesian approach we shall need a prior for the parameters and methods for dealing with their posterior distribution given Phase IIb data.

*A full problem formulation will require further assumptions:*

- Risk of safety problems vs dose,
- Costs of Phase IIb and Phase III trials,
- The benefit from a successful outcome in Phase III.
DIA (formerly PhRMA) Working Group

I shall describe work on the joint design of Phase II and Phase III trials by the Adaptive Programs stream of the Adaptive Design Scientific Working Group.

Members of the “Main model” team studying generic methods are:

Carl-Fredrik Burman (leader)
Zoran Antonijevic
Christy Chuang-Stein
Chris Jennison
Fredrik Öhrn
Nitin Patel
José Pinheiro
Alun Bedding

Other teams are working on specific application areas: Diabetes, Neuropathic pain, and Oncology.
Outline of the Phase IIb / Phase III process

1. Phase IIb trial

   Compare several doses against control

   Decide whether to proceed to Phase III

   If so, choose a dose and specify the Phase III sample size

2. Phase III trial

   Run two Phase III trials comparing the selected dose against control

   If both trials provide significant evidence of a treatment effect, we have a success!

Design questions:

Sample size for Phase IIb,

Decision making after Phase IIb: Stop/go, dose, Phase III sample size.
Outline of the optimal design process

To maximise expected net gain in a Bayes decision theoretic approach, we shall

Specify a model for dose response in Phase IIb and Phase III

Specify a prior distribution for parameters in the dose response model

Design the Phase IIb trial (doses, sample size, etc)

Run the Phase IIb trial

Find the posterior distribution of model parameters given Phase IIb data

Design the Phase III trials (stop/go, dose, sample size)

Run two Phase III trials

Analyse the Phase III data and see if the process has a successful outcome.

Here, the colour coding distinguishes between:

Model specification, Simulation, Design optimisation.
How can we optimise the design in this complex problem?

Optimising the overall design is a complicated problem.

For instance, the best way to design the Phase IIb trial depends on how we use the results of Phase IIb in designing Phase III.

The first step is to be able to work forwards through the whole process, using some (non-optimal) decision rules where necessary.

We shall consider how to:

1. Choose the prior distribution for dose response model parameters,
2. Simulate Phase IIb trial data,
3. Find the posterior distribution of model parameters given Phase IIb data,
4. Optimise the Phase III design given this posterior distribution,
5. Optimise the Phase IIb design.
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

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

- $\theta_1$: Mean response at dose zero (placebo effect)
- $\theta_2$: Increase in mean response from dose zero to a very high dose
- $\theta_3$: ED50, the dose achieving half this maximum increase
- $\theta_4$: Governs the steepness of the dose response curve
1. Specifying the prior distribution of dose response parameters

In our example, we have 7 active doses and the control. Suppose units are defined so that the control dose is $d_0 = 0$ and the active doses are $d_j = j$, $j = 1, \ldots, 7$. In reality, the values 0, 1, \ldots, 7 might represent doses of, say, 0, 50, \ldots, 350 mg.

So, the Emax model gives mean responses

$$\mu_j = \theta_1 + \theta_2 \frac{j \theta_4}{\theta_3 \theta_4 + j \theta_4}, \quad j = 0, \ldots, 7.$$ 

Suppose that, in the prior, we assume the four parameters are independent and

$$\theta_1 \sim N(a_1, b_1^2),$$
$$\theta_2 \sim N(a_2, b_2^2),$$
$$\theta_3 \sim N^+(a_3, b_3^2),$$
$$\theta_4 \sim N^+(a_4, b_4^2).$$

Here, $N^+$ denotes a normal distribution restricted to values greater than 0.01.
Specifying the prior distribution of dose response parameters

The plot shows a sample of 20 Emax dose response curves from the prior with

\[ a_1 = 2, \ b_1 = 1, \ a_2 = 4, \ b_2 = 3, \ a_3 = 4, \ b_3 = 2, \ a_4 = 4, \ b_4 = 0.5. \]

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

The curves with a negative treatment effect are coloured blue.
Specifying the prior distribution of dose response parameters

The investigators tell you that a treatment effect of 5 would be clinically meaningful — but they hope to see a higher effect.

There may be a placebo effect of 5 or 10 at dose zero.

A treatment effect (vs placebo) of 5 or 10 should be attainable.

A dose of 6 or 7 may be necessary to achieve this.

Opinion varies as to how steep the dose response curve might be.

Historical results for similar compounds at this stage indicate

\[ P\{\text{No positive treatment effect}\} = 0.4. \]

The R routine prior_sampler.R generates a sample of 20 dose response curves from a specified prior distribution.

See run_prior_sampler.R for an example of how to call this routine.

Find values of \( a_1, b_1, \ldots, a_4, b_4 \) that match the above expectations.
(1) Running R: Initial set up

You can run R in a particular directory on your computer.

It is advisable to create this directory first and copy into it the files provided on the memory stick.

After you start R, click on File, then on Change dir . . . .

Navigate to find the directory you want to be in and double click on its name.

As a check, you can type

   > getwd()

   to find the current directory.

If you are working in a directory containing copies of the files from the memory stick, these will appear in the list of options when you try to load a file or open a script.
(1) Running R: prior_sampler

To use the R routine `prior_sampler.R`, you need to load this into your workspace.

To do this, click on File, then on Source R Code. Navigate to the directory containing `prior_sampler.R`, then double click on this to load the code.

If you then type

```r
> ls()
```

You should see the functions “emaxmodel” and “prior_sampler” listed as being present in the workspace.

You can run commands in `run_prior_sampler.R` by opening this as a script.

Click on File, then on Open Script . . . . Navigate to `run_prior_sampler.R`, then double click on this to open a script.

If you highlight commands in the script and type Control R, these commands will run in the R Console.

You can edit the script file to modify the commands or add new ones.
(1) Running R: prior_sampler

The output from the commands in `run_prior_sampler.R` is a plot of 20 dose response curves generated from the specified prior.

Note that the plot is of the increase in mean response over dose zero, so all curves start at zero.

The command

```r
> x11()
```

in `run_prior_sampler.R` creates a new graphics window each time you run the script.

Graphics windows are overlaid, so you have to move the top ones aside to see the old ones below.

In modifying the prior so that the sample of dose response curves matches the specification, you need to know what each of the parameters $\theta_1, \ldots, \theta_4$ controls.

Look back to Slide 7 for an illustration of each parameter’s role.
(1) Notes on using Scripts

Having an open script file is a useful way to develop or modify a set of R commands.

If all you want to do is run the commands, you can simply load the file (click on File, then on Source R Code, etc.) and the full set of commands will be implemented.

With an open script, you can choose to run a few commands at a time, edit some lines and run them again, and so forth.

You can save changes to a script by clicking on File and Save while the script window is active.

I suggest that

(a) You keep the provided scripts unchanged, by saving using the Save as . . . option or by working with a copy of the original script.

(b) You close each script as you finish using it — it is easy enough to open it again if you need to.
2. Simulating Phase IIb responses

We assume a normal response distribution for patient response in Phase IIb — and the same response distribution in Phase III.

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

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

where \(\mu_j\) is given by the Emax model formula.

We shall consider Phase IIb designs in which 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, we have

\[ 0.3n_2 \text{ on dose zero,} \]
\[ 0.1n_2 \text{ on each active dose } j = 1, \ldots, 7. \]
Simulating Phase IIb responses

Given a Phase IIb design (e.g., sample size $n_2$) we wish to know properties such as

$$P\{\text{The Phase III trials are ultimately successful}\}$$

and expected total sample size.

We shall estimate such quantities by averaging over simulated Phase IIb data sets.

To create these data sets, we

- Simulate a vector $(\theta_1, \theta_2, \theta_3, \theta_4)$ from the prior,
- Calculate $\mu_j = E(X_{ij})$ at each dose $j$,
- Simulate responses $X_{ij}$ for subjects on each dose,

producing a number of data sets from hypothetical realisations of the Phase IIb trial.

*How should we run these simulations to serve our purposes most effectively?*
Simulating Phase IIb responses

We shall create data sets from realisations of a Phase IIb trial by

Simulating $(\theta_1, \theta_2, \theta_3, \theta_4)$ from the prior,

Calculating the means $\mu_j$,

Simulating responses $X_{ij}$ for subjects on each dose.

**Question 1.**

*We could generate one data set from each $(\theta_1, \theta_2, \theta_3, \theta_4)$ simulated from the prior — or a sample of several data sets for each $(\theta_1, \theta_2, \theta_3, \theta_4)$. Which approach is better for estimating the quantities of interest?*

**Question 2.**

*Suppose we wish to compare properties of two Phase IIb designs with different sample sizes, $n_2$. Are there useful ways to link the data sets generated for the two cases?*
3. Generating a sample from the posterior distribution of 
\[ \theta = (\theta_1, \theta_2, \theta_3, \theta_4) \] 
given Phase IIb data

Background information only: an implementation of this method is provided.

Combining the likelihood of the Phase IIb responses with the prior for \( \theta \) gives the posterior distribution for \( \theta \) after Phase IIb — which is not very tractable.

If we use Markov chain Monte Carlo simulation, we face the usual problems of

* Uncertainty about how rapidly the Markov chain sampler converges,
* Correlated samples.

For our choice of prior, the posterior distribution of \( \theta \) has some useful properties:

In the posterior distribution, the conditional distribution of \((\theta_1, \theta_2)\) given \((\theta_3, \theta_4)\) is bivariate normal.

Thus, we can integrate out \( \theta_1 \) and \( \theta_2 \) to get an expression for the joint density of \( \theta_3 \) and \( \theta_4 \), up to a multiplicative constant.
Sampling the posterior distribution of $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$

Once we have a formula for the joint posterior density of $(\theta_3, \theta_4)$, we can:

- Create an envelope for the density of $(\theta_3, \theta_4)$ on a two-dimensional grid,
- Use acceptance sampling to obtain exact, independent samples of $(\theta_3, \theta_4)$,
- Combine each sample of $(\theta_3, \theta_4)$ with a pair $(\theta_1, \theta_2)$ from the known conditional bivariate normal distribution.

A problem and a solution:

- We find may our envelope for the density of $\theta_1$ and $\theta_2$ is not high enough in places and some acceptance probabilities are greater than one.
- We can correct for this by giving importance sampling weights (greater than 1) to these values.
- Typically, only a few samples need a weight greater than 1.
Sampling the posterior distribution of $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)$

Denote by $\pi_{\theta|X}(\theta|x)$ the posterior distribution of $\theta$ given Phase IIb data $X = x$.

The R routine `posterior_sampler.R` generates a sample from $\pi_{\theta|X}(\theta|x)$.

If a sample size $S$ is specified, the output is a set of vectors $\theta^s$, $s = 1, \ldots, S$.

Each value $\theta^s$ has a weight $w_s$ (the importance weight, which is 1 in most cases).

Suppose we are interested in the conditional expectation of the function $f(\theta)$ given Phase IIb data $X = x$.

This is given by the integral

$$\int f(\theta) \pi_{\theta|X}(\theta|x) \, d\theta,$$

which we approximate by the sum

$$\sum_{s=1}^{S} \frac{w_s f(\theta^s)}{\sum_{s=1}^{S} w_s}.$$
Creating a set of data

The R routine `ph2_sampler.R` generates a sample of Phase IIb data for a specified parameter vector $\theta$ and sample size $n_2$.

The output is a vector of observed mean responses at doses 0, 1, …, 7.

*Use the commands in `run_ph2_sampler.R` to specify $\theta$ and $n_2$ and call the routine `ph2_sampler.R` — see next slide*

*The last two commands in `run_ph2_sampler.R` plot the mean responses against dose and superimpose the true dose response curve on this plot.*

The R routine `posterior_sampler.R` generates a sample of vectors $\theta$ from the posterior distribution of $\theta$ given observed Phase IIb data.

*Use the commands in `run_posterior_sampler.R` to sample from the posterior distribution of $\theta$ given the observed data generated by `ph2_sampler.R`.*

*Use the script `run2_posterior_sampler.R` to do more of the same — generating new Phase IIb data sets and sampling the posterior distributions.*
(3) Running R: ph2_sampler

To load `ph2_sampler.R`, into your workspace, click on File, then on Source R Code. Navigate to `ph2_sampler.R`, and double click on this to load the code.

If you then type

```r
> ls()
```

You should see that the functions “emaxmodel” and “ph2_sampler” are present in the workspace.

Open the script `run_ph2_sampler.R`, by clicking on File, then on Open Script . . . . Navigate to `run_ph2_sampler.R`, then double click on this to open the script.

Highlight commands in the script and type Control R to run these commands.

The `set.seed` command initialises the seed for the random number generator.

If you re-run the command

```r
> xbar=ph2_sampler(theta,n2)
```

by itself, the seed will have changed and you will get a new set of data.
(3) Running R: posterior_sampler

Having loaded `ph2_sampler.R` and run `run_ph2_sampler.R` to generate data `xbar`, load `posterior_sampler.R`, by clicking on File, then on Source R Code, etc.

Open `run_posterior_sampler.R` by clicking on File, then on Open Script . . . , etc.

Highlight commands in the script and type Control R to run these commands.

To run the whole script, press Control A (highlighting all the lines), then Control R.

You will be prompted to load the package `MASS` by double clicking on its name.

This package has a command for generating bivariate normal random variables.

You can also load this by clicking on Packages, then Load packages . . . , etc.

*If the plots produced by `run_posterior_sampler.R` are overlaid, move them around to see all the output.*

The script `run2_posterior_sampler.R` does not load `MASS` (it is already loaded).

You can run this repeatedly to see more examples.
Using the samples from the posterior distribution

For a particular $n_2$ we can:

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

Simulate Phase IIb data, given $\theta$.

Next, we shall use the samples representing the posterior distribution after Phase IIb to evaluate the Phase III options and choose the best option.

Then, we can average over replicates of Phase IIb to compute the expected net gain for a given $n_2$ and compare results to choose the best $n_2$. 
4. Optimising the Phase III design given Phase IIb data

The Phase III trials

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

We run two Phase III trials.

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

Responses are distributed as

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

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

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

(We assume the response distribution at each dose is exactly as in Phase IIb.)

If $H_{0j}$ is rejected at a significance level below $\alpha = 0.025$ in both trials, efficacy of dose $j$ is established.
Optimising the Phase III design

*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

\[
\begin{align*}
  c_2 &= 1, \\
  c_3 &= 1, \\
  g &= 12,000.
\end{align*}
\]

The meaning of 1 cost or gain unit may be $10,000$ to $50,000$, depending on the condition being investigated — so $g$ represents a multi-million dollar return.
Optimising the Phase III design

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 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 $\gamma(7) = 0.2$. Thus, the risk for dose $j$ is

$$\gamma_j = \left(\frac{j}{7}\right)^2 \times 0.2.$$

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 III design

At the end of Phase IIb

We must decide whether to proceed to run Phase III at all.

If we decide to run Phase III, we must select

- The dose to test in Phase III $j$,
- The sample size per arm, in each Phase III trial $n_3$.

We wish to make these decisions optimally

Overall, our optimality criterion is the expected net gain:

$$ g \times P\{ \text{Both Phase III trials significant at } \alpha = 0.025 \text{ and no safety problems} \} $$

$$ -n_2 c_2 - 4 E(N_3) c_3. $$
Optimising the Phase III design given Phase IIb data

**Evaluating Phase III options**

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

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

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

We estimate this conditional expected net gain by

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

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

The optimal Phase III design is that which maximises (1) over $j$ and $n_3$. 
(4) Optimising the Phase III design given Phase IIb data

**Evaluating Phase III options**

Run `create_theta_sample.R` (which is similar to `run_posterior_sampler.R`) to generate a set of Phase IIb data, then simulate a data array of vectors \( \theta^1, \ldots, \theta^{500} \) from the posterior distribution of \( \theta \).

Load the script `create_theta_sample.R` and run these commands. (If you have re-started R with an empty workspace, you will need to re-load `ph2_sampler.R` and `posterior_sampler.R` and the package MASS.)

Use Control A to highlight all the commands in `create_theta_sample.R` and Control R to run these commands.

The plots produced by the commands in `create_theta_sample.R` show

(i) The Phase IIb data, superimposed on the dose response curve from which the data were generated,

(ii) A contour plot of the posterior density of \((\theta_3, \theta_4)\).
(4) Running R: `create_theta_sample`

The resulting $500 \times 5$ array `theta_sample` contains vectors $\theta^1, \ldots, \theta^{500}$ sampled from the posterior distribution of $\theta$ given the Phase IIb data set, with an importance weight (usually 1) associated with each vector.

Type

```r
> theta_sample
```

to look at the values in the array `theta_sample`.

The final entry in each row is the importance sampling weight. Do any of these weights differ from 1?

You can give the command

```r
> max(theta_sample[,5])
```

to find the largest value of the numbers in column 5 of `theta_sample`. 
(4) Optimising the Phase III design given Phase IIb data

Evaluating Phase III options

The R script `e_cond_net_gain.R` evaluates terms that make up the conditional expected net gain

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

for a sample $\theta^1, \ldots, \theta^S$ and specified dose $j$ and Phase III sample size $n_3$.

Starting with the posterior sample $\theta^1, \ldots, \theta^{500}$ produced by `create_theta_sample.R`, run the R script `e_cond_net_gain.R` to calculate the probability of a successful Phase III outcome for each combination of

i) Dose $j \in \{1, \ldots, 7\}$, and

ii) Phase III sample size $n_3 \in \{50, 75, 100, 150, 200, 300, 400, 500\}$.

Hence, determine whether it is worthwhile to conduct the Phase III trials and, if so, which dose and sample size should be chosen.
(4) Running R: e_cond_net_gain

Load the script `e_cond_net_gain.R`, and run these commands to analyse the posterior distribution represented by `theta_sample.R`.

Use Control A to highlight the whole script and Control R to run these commands.

The script produces a number of $7 \times 8$ arrays, with the rows representing the doses $j = 1, \ldots, 7$ and the columns the 8 options for $n_3$.

To see $P\{\text{Two successful Phase III trials}\}$ for each combination of $j$ and $n_3$, averaged over the posterior sample of $\theta$ vectors, type

> epsuc

The probability of safety problems for each combination of $j$ and $n_3$ is shown by

> mgamma

What is the meaning of the output from the following command?

> (1-mgamma)*epsuc
(4) Running R: e_cond_net_gain

Look at the array of sampling costs for each combination of \( j \) and \( n_3 \).

\[ > \text{ecost} \]

Note that these values include the cost of \( n_2 \) observations in Phase IIb.

We can combine the variables \texttt{epsuc}, \texttt{mgamma} and \texttt{ecost}, to obtain the array of expected net gains

\[ > (1-\text{mgamma})\times\text{epsuc}\times\text{g-ecost} \]

Check this agrees with the array \texttt{egain} calculated by the script.

The location of the largest value in this array gives the optimal combination of dose \( j \) and Phase III sample size \( n_3 \).

How high does this largest value have to be for Phase III to be worthwhile?

Check you agree with the optimal dose and Phase III sample size reported by \texttt{e_cond_net_gain.R}.
5. Optimising the Phase IIb design

Once we know how to optimise the Phase III design for a given Phase IIb data set, we are ready to optimise Phase IIb.

Assume an Emax dose response model and a prior in which the Emax model parameters are independent with

\[
\begin{align*}
\theta_1 & \sim N(5, 10^2), \\
\theta_2 & \sim N(5, 10^2), \\
\theta_3 & \sim N^+(3.5, 7^2), \\
\theta_4 & \sim N^+(1, 1^2),
\end{align*}
\]

where \(N^+\) denotes a normal distribution restricted to values greater than 0.01.

Let response distributions, gain and cost functions, and the risk of safety problems be as defined previously.

Given the Phase IIb data we can apply the methods we have just seen to find the optimal decisions regarding Phase III.
(5) Running R: e_net_gain

**Evaluating Phase IIb options**

The R script `e_net_gain.R` reads in data from the file `posterior_samples` to create a $6 \times 500 \times 500 \times 5$ data array.

These data were produced by simulating 500 Phase IIb data sets for each of 6 $n_2$ values. For each data set, a sample $(\theta^1, \ldots, \theta^{500})$ with related importance weights was simulated from the posterior distribution of $\theta$.

The script `e_net_gain.R` goes on to evaluate the expected net gain

$$g \times P\{\text{Both Phase III trials significant at } \alpha = 0.025 \text{ and no safety problems}\}$$

$$-n_2 c_2 - 4 E(N_3) c_3$$

for Phase IIb designs using each possible choice of $n_2$.

Here, the decision whether to conduct Phase III trials and, if so, the choice of dose and sample size $n_3$ optimise this expected gain.
(5) Running R: e_net_gain

Evaluating Phase IIb options

The script `e_net_gain.R` averages the expected gain (optimised over Phase III designs) for each of the 500 Phase IIb data sets from a given $n_2$.

This allows us to compare the benefits of different Phase IIb sample sizes, $n_2$, and choose the optimal value from the set \{50, 100, 200, 300, 400, 500\}.

*Apply the commands in `e_net_gain.R` to find the optimal choice of $n_2$ in this formulation of the overall design problem.*

To do this, first load the routines in `e_net_gain_routines.R` and `e_net_gain.R` by clicking on File, then on Source R Code, etc.

Next, click on File and Source R Code and load `run_e_net_gain.R` to run this code.

There are a lot of calculations to carry out and you should see results appear gradually (one set every few minutes) for one value of $n_2$ at a time.
(5) Running R: e_net_gain

For each $n_2$, there is output giving estimates, and associated standard errors, of:

- The expected gain,
- The Probability of two successful Phase III trials, $P\{\text{Two successful Phase III trials}\}$ discounted for the risk of safety failure,
- The expected cost of Phase III sampling.

For each $n_2$, histograms are drawn to show the distribution of the optimal dose and the optimal Phase III sample size $n_3$ over the 500 Phase IIb data sets.

We find the optimal choice of $n_2$ in the overall design problem by comparing the expected gain under different choices of $n_2$. What is the optimal $n_2$?

The histograms of optimal dose and the optimal Phase III sample size for this optimal $n_2$ are drawn again at the end.
(5) Running R: e_net_gain

The final commands in e_net_gain.R draw plots showing the relationship between the posterior means of various quantities and the optimal dose for Phase III.

These quantities are

- The posterior mean of the treatment effect, $E(X)$,
- The posterior probability of two successful Phase III trials,
- The posterior mean of the expected total gain.

For each Phase IIb data set, the quantity is evaluated at the dose selected for Phase III.

Explore the output from e_net_gain.R to see how the success probability and Phase III sampling costs behave as $n_2$ increases.

Can you think of reasons why the final histograms and plots look the way they do?
6. Recap: 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 $j$,
- The Phase III sample size $n_3$.

*We aim to optimise:*

- The choice of $n_2$,
- The rule for deciding whether to proceed to Phase III,
- The rule for choosing $j$ and $n_3$. 
Optimisation algorithm

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 $n_2$. 

\begin{align*}
\begin{array}{c|c|c|c}
  n_2 & \text{Replicates of Phase II data} & \text{Sample posterior model distribution} & d_j \text{ and } n_3 \\
\end{array}
\end{align*}
Results for a worked example

Consider a problem with 7 active dose levels \(d_j = j, j = 1, \ldots, 7\).

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

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

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

\[
\begin{align*}
\gamma_1 &= 0.004, & \gamma_2 &= 0.016, & \gamma_3 &= 0.037, & \gamma_4 &= 0.065, \\
\gamma_5 &= 0.10, & \gamma_6 &= 0.15, & \gamma_7 &= 0.2.
\end{align*}
\]
Results for a simple example

We optimise over Phase III sample sizes

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

Comparing Phase IIb designs, we find:

<table>
<thead>
<tr>
<th>( n_2 )</th>
<th>( E(\text{Net gain}) )</th>
<th>( n_2 )</th>
<th>( E(\text{Net gain}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>4,375</td>
<td>200</td>
<td>4,630</td>
</tr>
<tr>
<td>50</td>
<td>4,450</td>
<td>250</td>
<td>4,635</td>
</tr>
<tr>
<td>75</td>
<td>4,520</td>
<td>300</td>
<td>4,650</td>
</tr>
<tr>
<td>100</td>
<td>4,555</td>
<td>350</td>
<td>4,645</td>
</tr>
<tr>
<td>125</td>
<td>4,575</td>
<td>400</td>
<td>4,645</td>
</tr>
<tr>
<td>150</td>
<td>4,600</td>
<td>450</td>
<td>4,630</td>
</tr>
<tr>
<td>175</td>
<td>4,615</td>
<td>500</td>
<td>4,605</td>
</tr>
</tbody>
</table>

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:

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

* Two successful Phase III trials and no safety problems.
Accuracy of comparisons

Comparisons of Phase IIb designs are based on:

- 500 replicates of Phase IIb data sets,
- 500 samples from posterior distribution of $\theta$ for each Phase IIb data set.

<table>
<thead>
<tr>
<th>$n_2$</th>
<th>$E(\text{Net gain})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>250</td>
<td>4,635</td>
</tr>
<tr>
<td><strong>300</strong></td>
<td><strong>4,650</strong></td>
</tr>
<tr>
<td>350</td>
<td>4,645</td>
</tr>
<tr>
<td>400</td>
<td>4,645</td>
</tr>
</tbody>
</table>

Estimated values of $E(\text{Net gain})$ are subject to sampling error with

$$\text{Standard errors of } E(\text{Net gain}) \approx 200.$$  

However, coupling the simulations of Phase IIb data sets leads to

$$\text{Standard errors of differences in } E(\text{Net gain}) \approx 10.$$
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:

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.

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

Consider the problem formulation and the methods we have used to solve the optimal design problem.

This problem might be regarded as about the simplest possible formulation that has sufficient ingredients to make a solution possible.

**Question 1.**

*Which aspects of the problem would you like to modify in order to achieve a more realistic model for the Phase II – Phase III process?*

**Question 2.**

*Which of these modifications do you believe to be computationally feasible using the approach that we have followed?*
(7) Implementing some extensions

The “net present value” function `npvgain` in `e_net_gain_routines.R` takes arguments

- \( n2 \), the Phase IIb sample size,
- \( vn3 \), the vector of possible Phase III sample sizes,
- \( effect \), the treatment effect at the dose under consideration.

One might wish to let this gain function depend on the time taken to reach a conclusion and the treatment effect size.

Explore this by modifying the function `npvgain` to reflect that:

Larger Phase III trials eat into patent lifetime and reduce the period in which a new drug earns income for the manufacturer,

The income a drug earns depends on how effective it is (over and above showing that it has at least some effect).

If you want some ideas, one alternative definition is available in `alt_npvgain.R`
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.

Simulations from the posterior distribution nested within replicates of Phase IIb data constitute a substantial computational task. However, there are several routes to improving computational efficiency and making this task feasible.

There are many directions in which to elaborate the problem we have studied. Some of these elaborations can be handled with a similar amount of computation — but others may be more challenging!