Effective design of Phase II and Phase III 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

The Adaptive Progams stream of the Adaptive Design Scientific Working Group has been studying the joint design of Phase II and Phase III trials.

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 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
   - Results for an initial example

3. Extensions and methods for improving computational speed

4. Results when the Phase III trial is group sequential
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

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

- $\theta_1$: 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
Dose response model and prior for Bayesian analysis

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

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

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

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

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 chosen prior.

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 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

$$0.3n_2 \quad \text{on dose zero},$$
$$0.1n_2 \quad \text{on each active dose } j = 1, \ldots, 7.$$
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 $\mu_j - \mu_0 > 0$.

If $H_{0j}$ is rejected at a significance level below $\alpha = 0.025$ in both trials, efficacy of dose $j$ 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 Phase III incurs a cost of $c_3$ per subject.

In our example, we shall take

\[ c_2 = 1, \]
\[ c_3 = 1, \]
\[ g = 12,000. \]

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.
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 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 \( \theta \), 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

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

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

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

We estimate this conditional expected net gain by

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

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 \( n_3 \).
Results for a simple 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 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:

<table>
<thead>
<tr>
<th>( n_2 )</th>
<th>( E(\text{Net gain}) )</th>
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<th>( E(\text{Net gain}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>4,375</td>
<td>200</td>
<td>4,630</td>
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<tr>
<td>50</td>
<td>4,450</td>
<td>250</td>
<td>4,635</td>
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<td>75</td>
<td>4,520</td>
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<tr>
<td>100</td>
<td>4,555</td>
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<td>4,645</td>
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<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>
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<tr>
<td>50</td>
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<td>861</td>
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</tr>
<tr>
<td>100</td>
<td>0.460</td>
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<td>4,555</td>
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<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>
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</tr>
<tr>
<td>350</td>
<td>0.487</td>
<td>847</td>
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<tr>
<td>400</td>
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<td>840</td>
<td>4,645</td>
</tr>
<tr>
<td>450</td>
<td>0.492</td>
<td>823</td>
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</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>
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<tr>
<td>250</td>
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</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.
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.
Computational problems and possible solutions

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

**Sampling the posterior distribution**  At the 2012 PSI conference, Jane Temple talked about direct sampling from the posterior distribution of Emax parameters.

**Multiple use of samples from the posterior model distribution**

Rather than repeat 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**

More complex Phase III designs (group sequential or multi-armed) can be evaluated up-front on a grid of parameter values, creating a look-up table for general cases. This re-use of information for different interim states has a parallel with the dynamic programming (backwards induction) optimisation algorithm.
Results when Phase III has a group sequential design

Consider the previous example but now with one group sequential Phase III trial and a required significance level of $0.0005 \ (\approx 0.025^2)$.

Members of the $\rho$-family of one-sided, error spending designs (Jennison & Turnbull, 2000, Ch. 7) are known to be highly efficient (Barber & Jennison, *Biometrika*, 2002).

We use this form of design with 5 groups and $\rho = 2$.

With the same values of $n_3$ for possible *maximum* Phase III sample sizes, we find:

<table>
<thead>
<tr>
<th>$n_2$</th>
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</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5,240</td>
<td>200</td>
<td>5,280</td>
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<tr>
<td>50</td>
<td>5,270</td>
<td>250</td>
<td>5,260</td>
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<tr>
<td>75</td>
<td>5,300</td>
<td>300</td>
<td>5,255</td>
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<tr>
<td><strong>100</strong></td>
<td><strong>5,300</strong></td>
<td>350</td>
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<tr>
<td>125</td>
<td>5,290</td>
<td>400</td>
<td>5,215</td>
</tr>
<tr>
<td>150</td>
<td>5,290</td>
<td>450</td>
<td>5,190</td>
</tr>
<tr>
<td>175</td>
<td>5,280</td>
<td>500</td>
<td>5,155</td>
</tr>
</tbody>
</table>
Results when Phase III has a group sequential design

The Expected net gain is considerably higher (by over 600 units) than with fixed sample size Phase III trials.

The optimal Phase IIb sample size is smaller (100 rather than 300).

The group sequential Phase III design means it is less crucial to have an accurate estimate of the treatment effect on which to base the Phase III sample size.
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!