Optimising the design of successive Phase IIb and Phase III trials

Additional slides

Christopher Jennison

Department of Mathematical Sciences,

University of Bath, UK

http://people.bath.ac.uk/mascj

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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 $\boldsymbol{\theta} = (\theta_1, \theta_2, \theta_3, \theta_4)$ has

$$\theta_1 \sim N(5,\ 10^2), \qquad \theta_2 \sim N(5,\ 10^2),$$

$$\theta_3 \sim N^+(3.5,\ 7^2), \quad \theta_4 \sim N^+(1,\ 1).$$

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 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

$$\gamma_1 = 0.004, \quad \gamma_2 = 0.016, \quad \gamma_3 = 0.037, \quad \gamma_4 = 0.065,$$

$$\gamma_5 = 0.10, \quad \gamma_6 = 0.15, \quad \gamma_7 = 0.2.$$

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(Net gain)	n_2	E(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 $E($Net gain$)$ values are made up from:

n_2	$P($Overall success$^*)$	$4\,E(N_3)$	$E($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.

Accuracy of comparisons

Comparisons of Phase IIb designs are based on:

500 replicates of Phase IIb data sets,

500 samples from posterior distribution of $\boldsymbol{\theta}$ for each Phase IIb data set.

n_2	$E(\text{Net gain})$
250	4,635
300	**4,650**
350	4,645
400	4,645

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

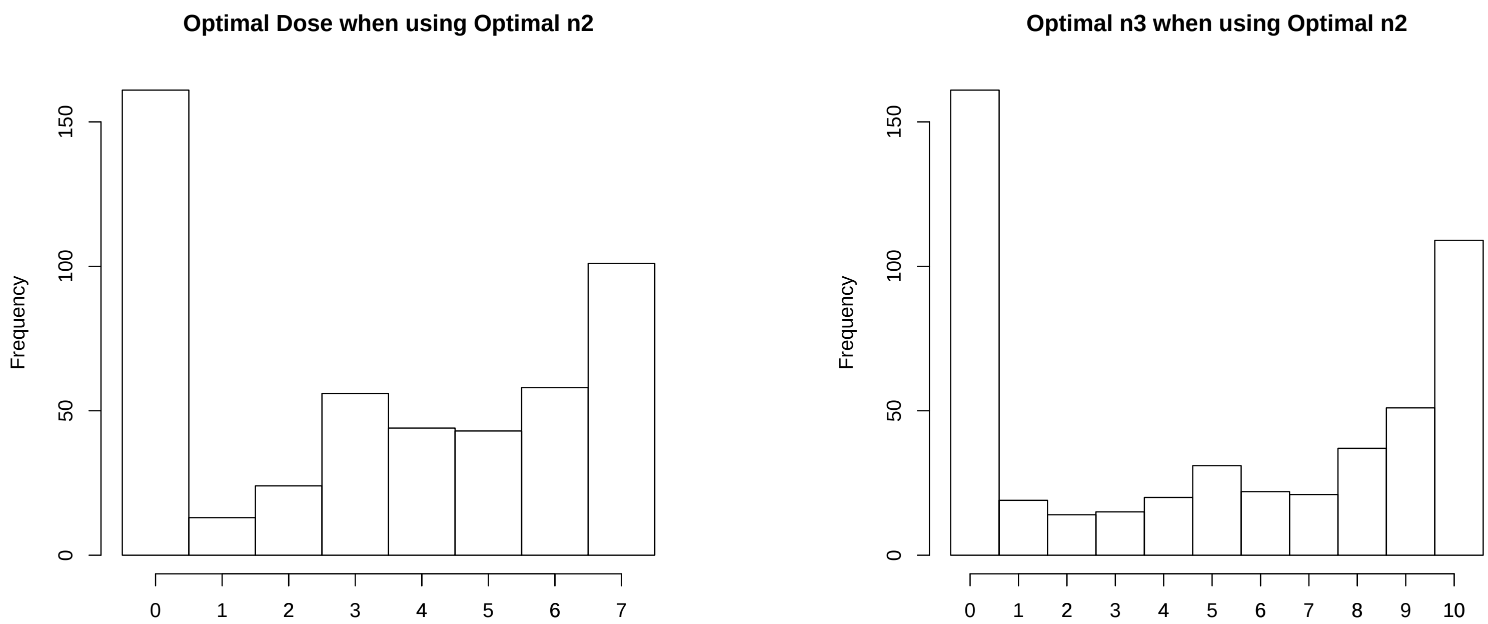
Standard errors of $E(\textit{Net gain}) \;\approx\;$ *200.*

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

Standard errors of differences in $E(\textit{Net gain}) \;\approx\;$ *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:

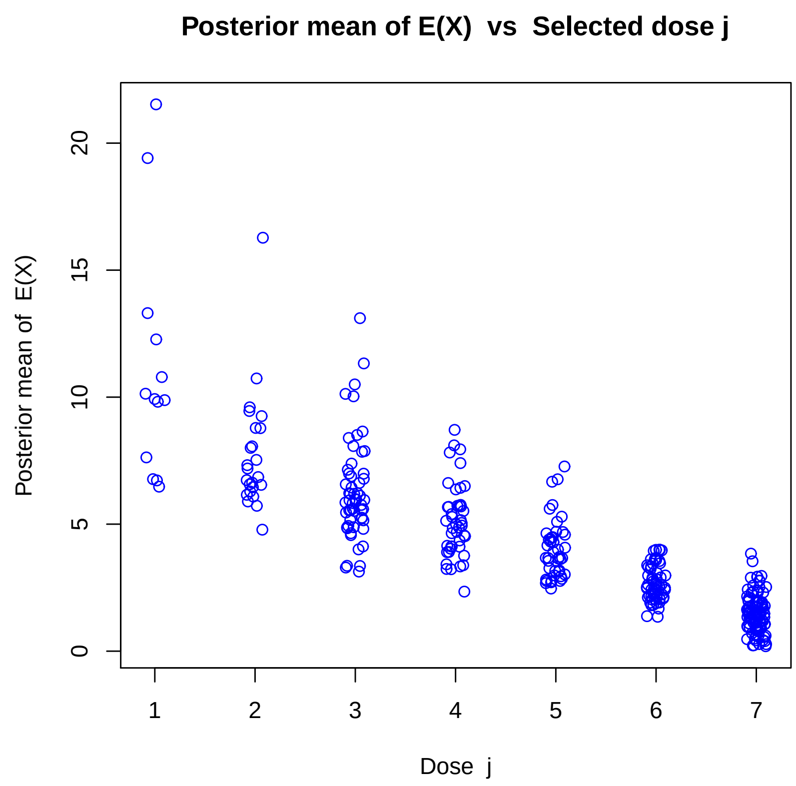


The risk of safety problems guides the decision towards lower doses.

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.

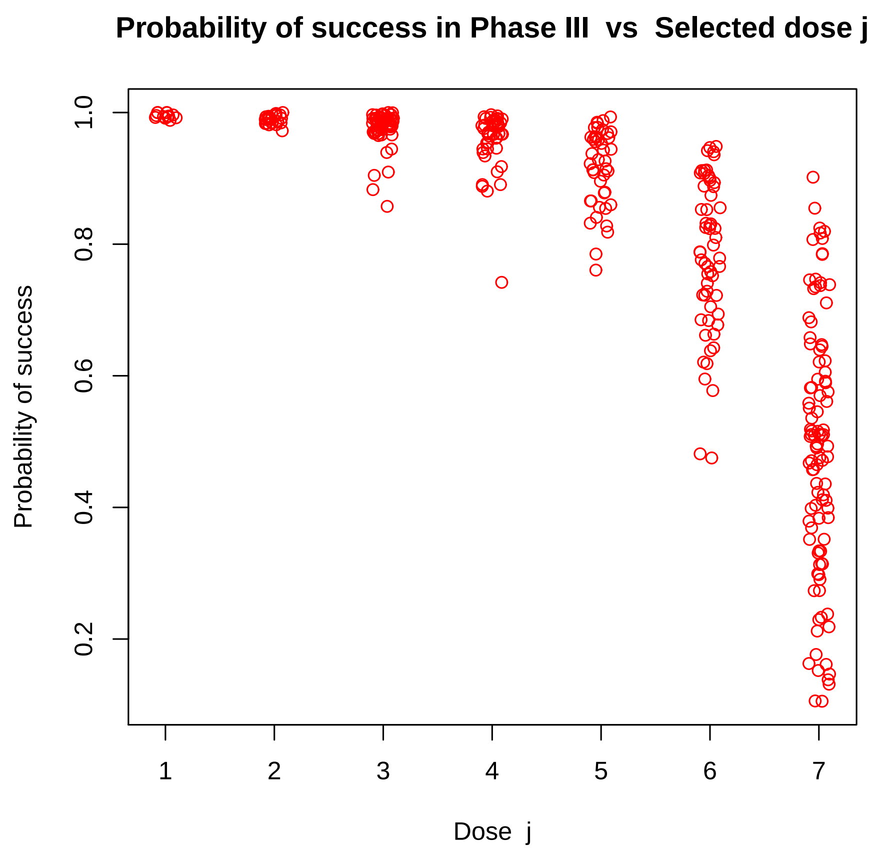


A high dose is selected when the posterior samples of the dose response curve show modest treatment effects.

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 of Emax parameters Jane Temple and I have developed a method for sampling directly from the posterior distribution.

Multiple use of samples from the posterior model distribution

Rather than repeat simulations to sample the posterior distribution of θ 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 ρ-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 $\rho = 2$.

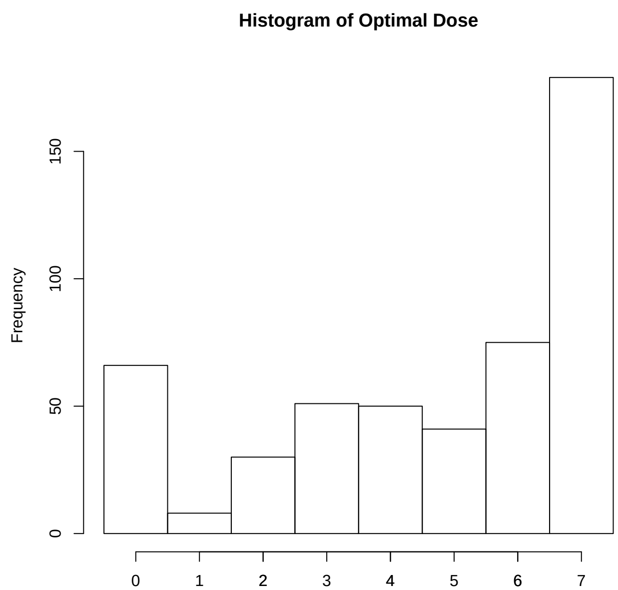
With the same values of n_3 for possible *maximum* Phase III sample sizes, we find:

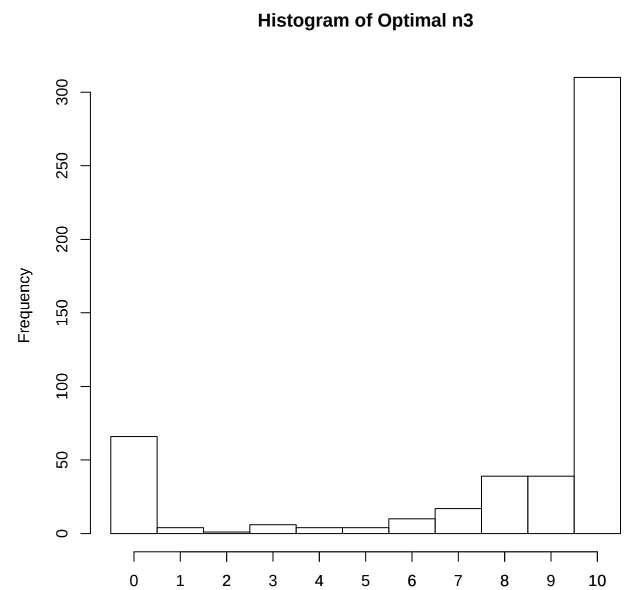
n_2	$E($Net gain$)$	n_2	$E($Net gain$)$
25	5,240	200	5,280
50	5,270	250	5,260
75	5,300	300	5,255
100	**5,300**	350	5,235
125	5,290	400	5,215
150	5,290	450	5,190
175	5,280	500	5,155

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!