

# Design and Analysis of Adaptive Clinical Trials:

## Addressing the Study Goals

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**19 December 2020**

# Decision making in clinical trials

What data should we collect?

- How many subjects?
- Which dose for each subject?

How to proceed after a Phase I or Phase II trial

- Go / No go?
- The dose to take forward?

**The solution needs:**

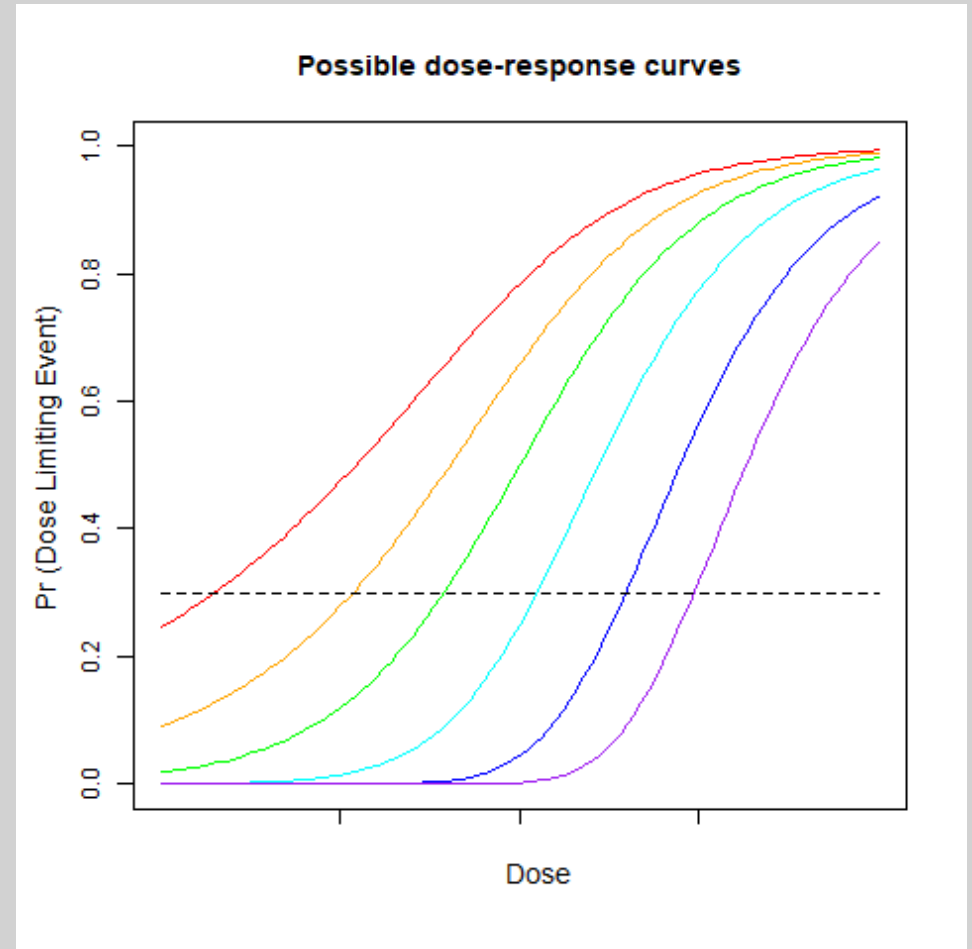
- **A model for the data**
- **A well-formulated objective**

**– recognising the role of this study in the overall drug development process.**

# 1. Phase I: “First in Human” trials

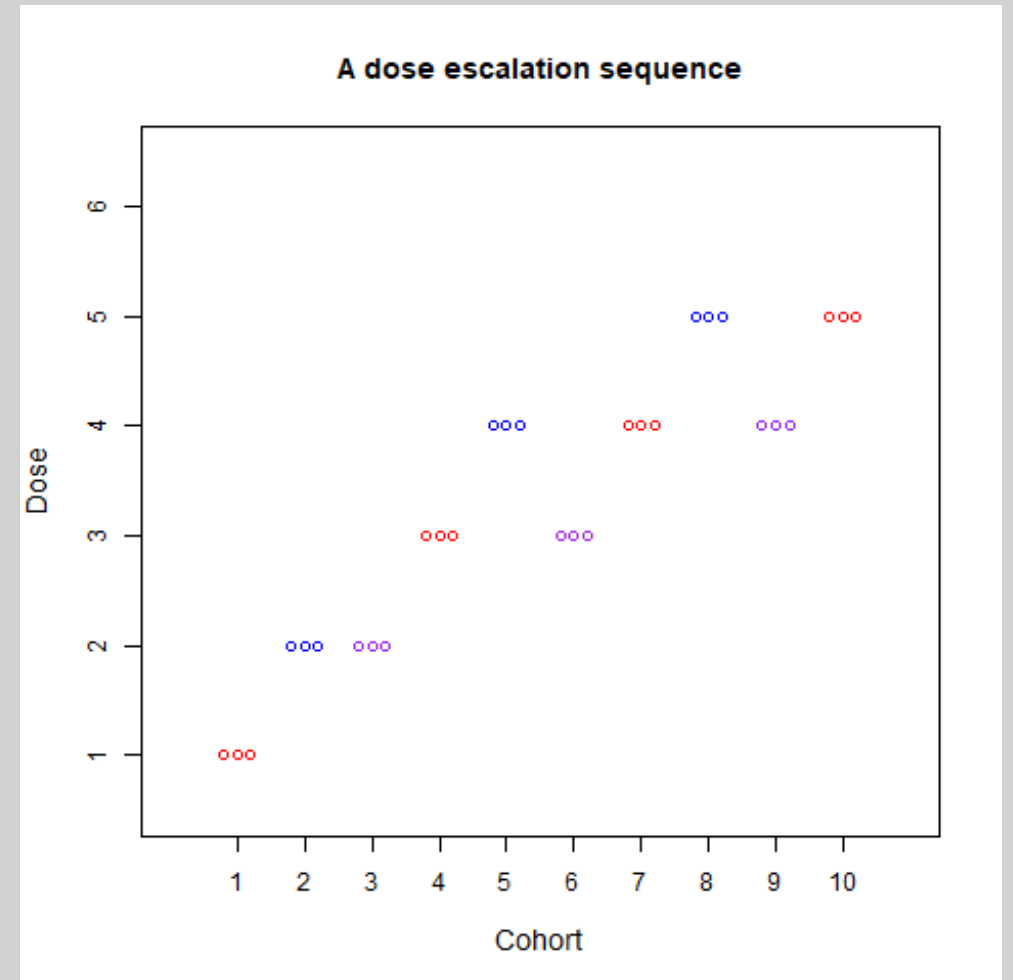
In a trial with healthy volunteers, we aim to:

- Find the maximum safe dose;
- Maintain safety of study participants.



# Design of a First in Human trial

- Treat cohorts of 3 patients
- Give cohort 1 the lowest dose
- Increase the dose for each cohort if it is safe to do so
- Select the dose for which  $\text{Pr}(\text{Dose limiting event})$  is closest to 0.3.



# Optimising the design: Bayes decision theory

Specify a model for the dose-response curve.

Elicit a prior distribution for the dose-response curve.

Define an objective function to be minimised, for example,

$$G = |p^* - 0.3| + \lambda \times (\text{Number of observed dose limiting events})$$

where  $p^*$  denotes  $\text{Pr}(\text{Dose limiting event})$  for the selected dose.

Choose doses for successive cohorts to **minimise the average value of  $G$** .

# Optimising by Dynamic Programming

There are many millions of possible sequences of dose assignments and outcomes.

Nevertheless, Lizzi Pitt, a University of Bath PhD student, has been able to compute the unique optimum design for a given statistical model and objective function  $G$ .

Additionally, modelling the data that arise in the Dynamic Programming algorithm allows rapid computation of an almost optimal trial design.

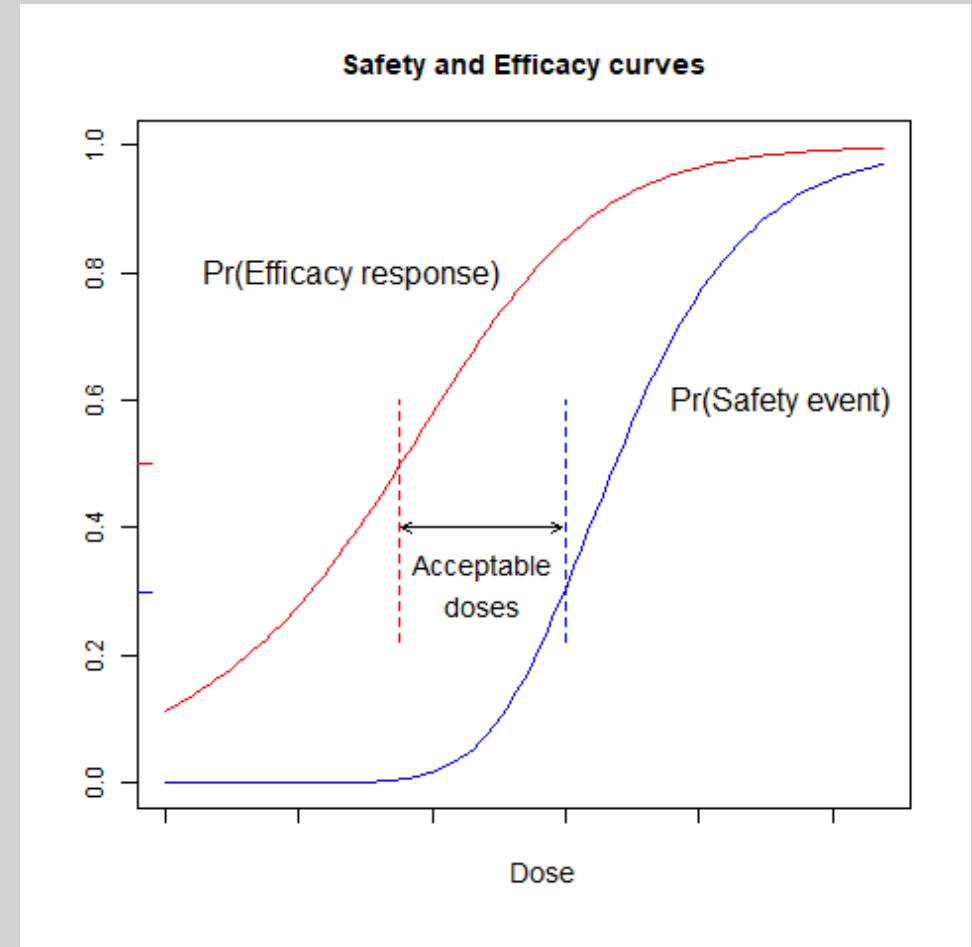
# A Phase I trial with safety and efficacy endpoints

Suppose an acceptable dose should have

- $\Pr(\text{Efficacy response}) > 0.5$ ;
- $\Pr(\text{Safety event}) < 0.3$ .

We wish to consider doses meeting these criteria in the subsequent Phase II trial.

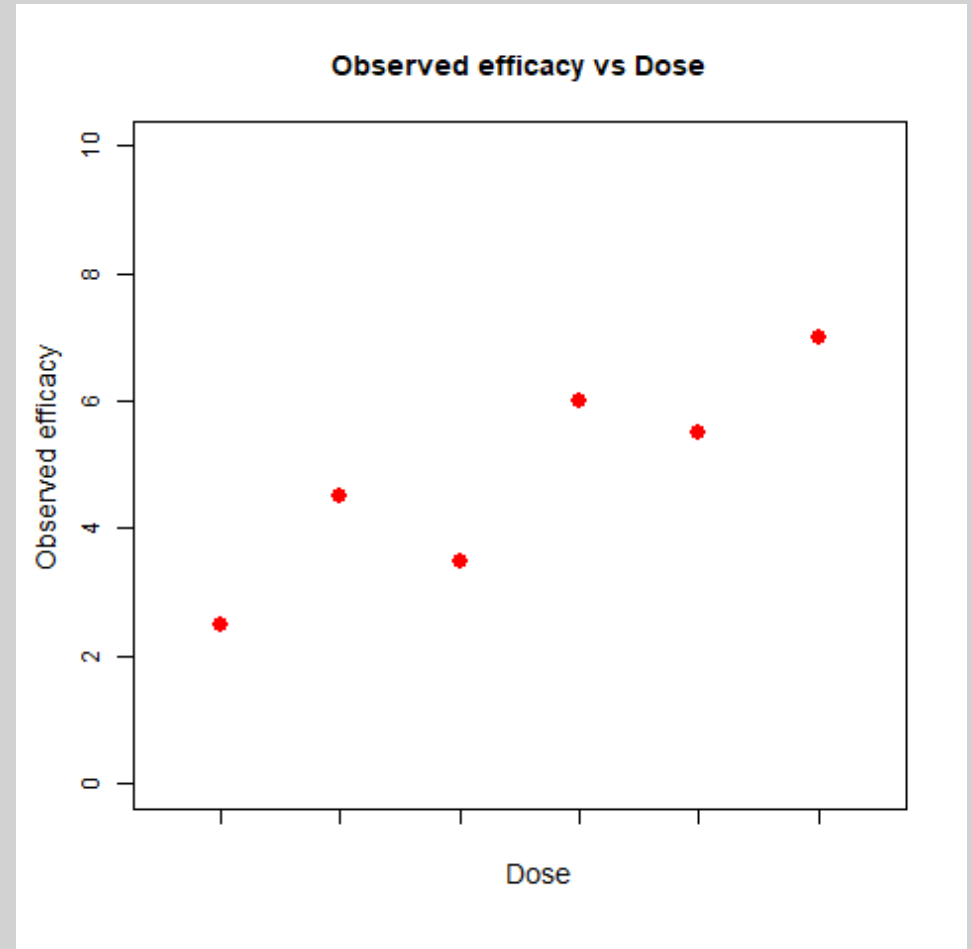
Again, optimal trial designs can be found.



## 2. Dose selection after Phase II

After a Phase II trial is completed:

- Is a Phase III trial worthwhile?
- Which dose, or doses, should be tested vs control?
- How large should the Phase III trial be?





# Problem formulation

## ***Ultimate goal***

A positive Phase III trial and regulatory approval of the new drug.

## ***Objective function to maximise***

$C \times I_{Success}$  – Cost of Phase III trial

Where

$I_{Success} = 1$ , If Phase III trial  
successful  
0, Otherwise.

## ***Statistical model***

Efficacy vs Dose curve, e.g., an Emax model

Posterior distribution for model parameters,  
given Phase II data

## ***Decision options***

- Phase III: Yes or no?
- Which dose to test in Phase III
- Sample size for Phase III trial

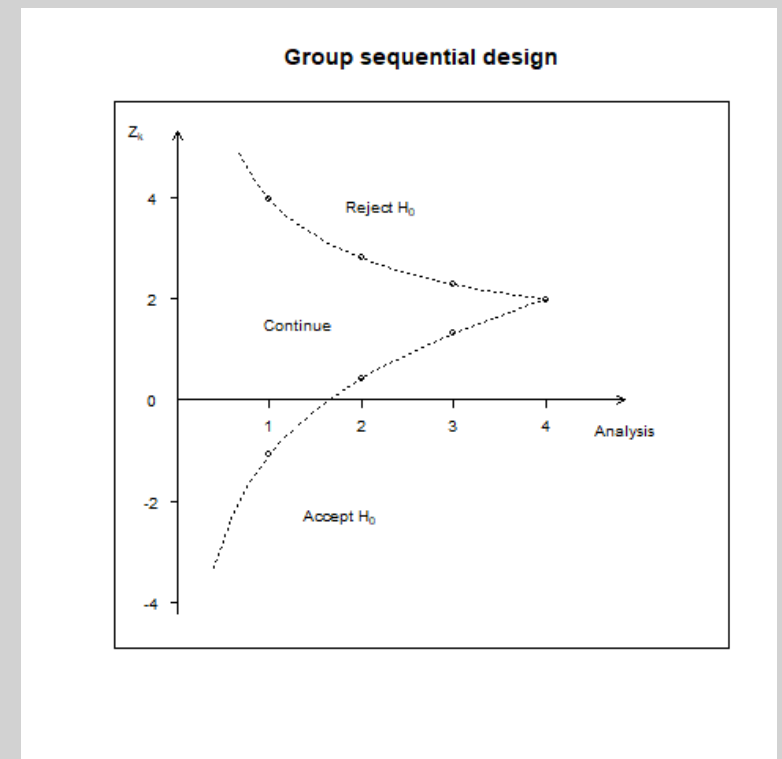
# Optimising Phase II and Phase III trials

Robbie Peck, a University of Bath PhD student, has produced methods for joint optimisation of Phase II and Phase III trials.

## *In a group sequential Phase III trial:*

Maximum sample size is set to give high power for a small, but clinically relevant, treatment effect.

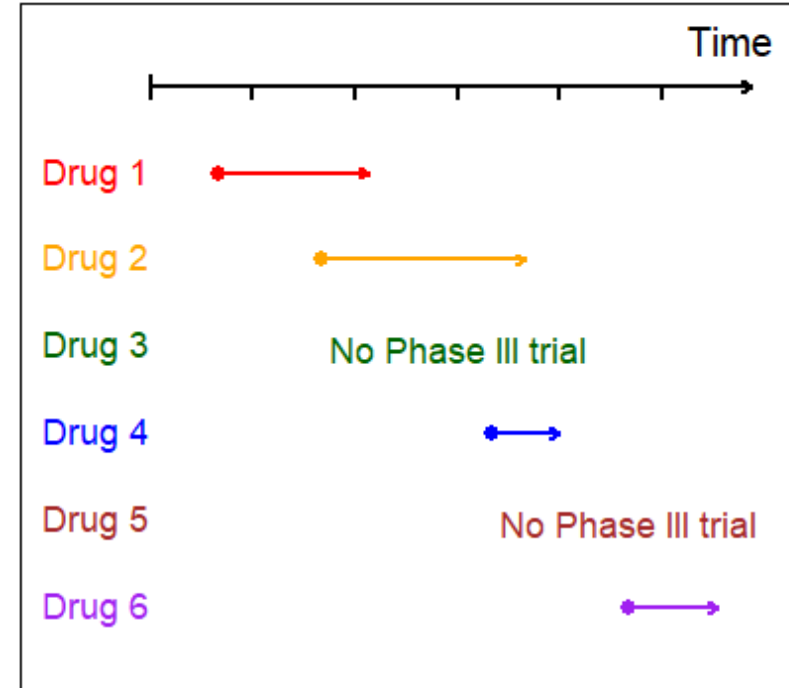
However, the trial will most likely stop early with a smaller sample size when the treatment effect is larger than this.



# Portfolio management

A company must share finite resources between compounds, at different stages of development

- Robbie Peck worked with Nitin Patel (Cytel) and CJ (Univ of Bath) to develop a model this process and optimize its management
- Dynamic Programming can be used to solve complex portfolio problems.



## 3. Phase III “enrichment” trials

A new treatment is expected to be particularly effective for patients exhibiting a certain biomarker.

- Should we restrict the Phase III trial biomarker positive patients?

An “Enrichment trial” starts by recruiting from the full population.

The trial “adapts” and focuses on biomarker positive patients if interim data support this change.

### Designing an adaptive enrichment trial

#### *Adaptive trial design*

- Multiple hypothesis testing
- Combination tests (to combine data from before and after the interim analysis)

#### *Gain function to maximise, proportional to:*

- The size of population in which the new treatment is proved to be effective
- The average treatment effect in this population.

# Optimising an enrichment design

## *The statistical model*

Treatment effect (new vs control)

In biomarker positive patients:  $\theta_1$

In biomarker negative patients:  $\theta_2$

Prior distribution for  $(\theta_1, \theta_2)$

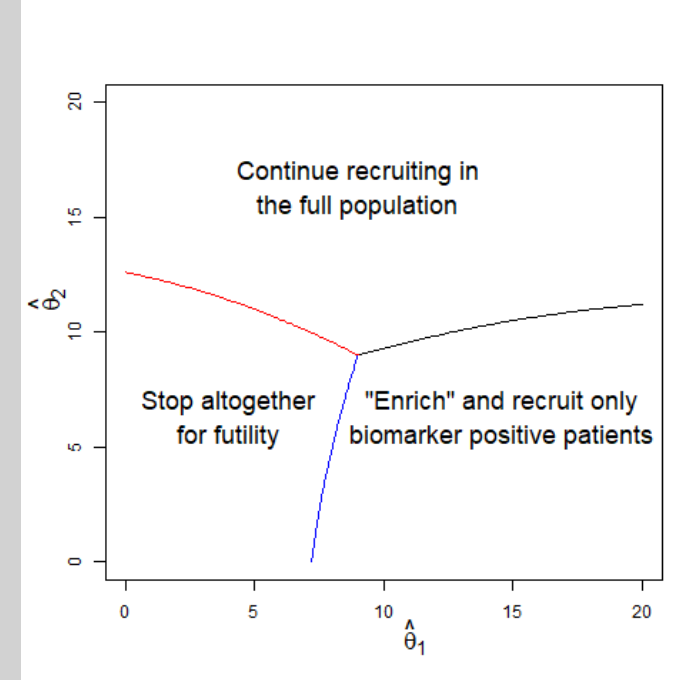
## *The decision to enrich*

is based on interim

estimates  $(\hat{\theta}_1, \hat{\theta}_2)$

University of Bath PhD student, Thomas Burnett, has derived Bayes optimal enrichment designs.

*(Statistics in Medicine, 2020)*



We have assessed the benefits of such designs:

These depend strongly on prior beliefs or assumptions about  $\theta_1$  and  $\theta_2$  – but there clearly are situations where adaptive enrichment designs are appropriate.

# Conclusions

Clinical trial data are expensive to obtain.

The duration of clinical trials has a major impact on the financial return to the developer of a new treatment.

Efficient trial designs can be created at all phases of development, given

- A model for the trial in question;
- A well-defined objective to optimise.