Optimal Decision Making in Drug Development

Peck, Robbie

Award date:
2020

Awarding institution:
University of Bath

Optimal Decision Making in Drug Development

submitted by

Robert Peck

for the degree of *Doctor of Philosophy*

of the

University of Bath

Department of Mathematical Sciences

Dec. 2019

Declaration of any Previous Submission of the Work

The material presented here for examination for the award of a higher degree by research has not been incorporated into a submission for another degree.

.....

Robert Peck

Declaration of Authorship

I am the author of this thesis, and the work described therein was carried out by myself personally.

.....

Robert Peck

Summary

This thesis deals with quantitative decision making in a variety of different situations in drug development. In these different situations, optimal decision strategies may be derived and the value of different adaptive or model-based approaches may be quantified.

We primarily use examples of Phase II/III programmes and portfolios of Phase III trials. Bayesian decision theory is a method that may be used to derive optimal decision rules given a gain function that aims to model the net present value of various assets to a trial sponsor. Deriving these optimal decision rules may be done using the method of dynamic programming with numerical integration routines. We investigate the benefit of adaptive methods such as group sequential designs or combination tests, or model-based approaches such as MCP-Mod to programmes and portfolios.

Our results show that Bayesian decision theory coupled with the method of dynamic programming may find optimal decision rules in a variety of settings in drug development. These optimal decision rules may involve the choice of dose to take forward for a Phase III trial given Phase II data in a Phase II/III programme, or the choice of sample size for a trial in a portfolio of Phase III trials. It was found in simulation studies that group sequential designs may add value to a drug development programme or portfolio. Furthermore, the use of combination tests may add a smaller amount of value to a drug development programme.

The problems discussed in this thesis are relevant to the running of clinical trials in industry. The methods we discuss may provide frameworks for the use of quantitative methods to help inform decision making in drug development.

Acknowledgements

I would like to thank the following people and organisations for guidance, support, and encouragement when writing this thesis. Firstly, I thank Prof. Chris Jennison for using his expertise and time to teach me about the fascinating field of adaptive designs for clinical trials, and for his guidance over the last 4 years in helping direct my research. I am grateful for the staff and students in the Department of Mathematical Sciences at the University of Bath for creating an enjoyable and inspiring working atmosphere. In particular I thank Dr. Theresa Smith and Dr. Karim Anaya-Izquierdo for their helpful comments during confirmation and the management team of Statistical Applied Mathematics at Bath (SAMBa) who have worked hard to create a successful Centre of Doctoral Training (CDT) that allowed me and other PhD students to flourish. I am grateful for the funding the Engineering and Physical Sciences Research Council (EPSRC) provided through SAMBa under the project EP/L015684/1 for me to pursue a PhD.

Much of this thesis has been motivated by industrial problems with many of the ideas coming from discussions with Dr. Alun Bedding (Roche, UK), Mr. Jaydeep Bhattacharyya, and Prof. Nitin Patel (Cytel, USA). I thank Alun for the meetings we have had over the last 4 years in Welwyn Garden City, Bath, and at conferences across Europe. Many of his comments about my research have been useful in providing context to the problems I am tackling. I also thank both Jaydeep and Nitin for providing me with two interesting problems during my internship in Cambridge MA and allowing me to live and work in an interesting city for a few months. These problems motivated the final two chapters of this thesis.

Finally, I say a special thanks to my friends both in and outside the mathematics department in Bath and my family for support, encouragement, and for making my time at university an enjoyable and nourishing experience.

Contents

A Brief Introduction

The development of new drugs

Great advances have been made in medicine in the last century. Many medical conditions now have treatment options which aim to cure, slow the progression, or manage the symptoms of the condition. However there are still conditions with no satisfactory treatment options, and further progress can be made with current treatments.

Randomised controlled trials may be used to establish the efficacy and safety of newly developed treatments by comparing the new treatment to the current standard treatment. This involves randomly assigning patients to several treatment groups through several phases. This randomisation may be double-blinded, which means neither the patient or investigator knows the treatment group of the patient.

A double-blind randomised control trial is a scientifically rigorous method of hypothesis testing and is considered the gold standard trial for evaluating the efficacy of a drug.

The development of a drug may depend upon the therapeutic area but is often characterised by a number of clinical phases. These phases of drug development are listed below.

Phase I clinical trials are the first to involve a small number of human patients and aim to make some initial assessment about the drug. In particular, the safety and tolerability of the drug are studied.

Phase II clinical trials aim to identify if the treatment is efficacious whilst also considering the safety and tolerability. Several treatments or doses of the same treatment may be considered. This phase uses a moderate number of patients.

Phase III aims to provide confirmatory evidence that the treatment is better than the current standard treatment and is safe. A larger number of patients are used. A statistical framework of hypothesis testing is applied at this stage and results submitted to regulatory bodies for approval to market the treatment.

Phase IV aims to monitor the effectiveness and safety of the marketed drug. Regulatory agencies may refer to these trials as post marketing surveillance trials.

Decision making in drug development

The pharmaceutical industry lags behind other industries in the uptake of quantitative methods in making decisions. Antonijevic in Antonijevic (2014) notes that for example, there is a lack of utilisation of modelling, simulation, and decision analysis. A possible reason for may relate to the recent history of the industry. During the blockbuster era, getting regulatory approval was easier due to less stringent safety requirements. Furthermore companies could target diseases that affected large populations such as heart disease, pain, or depression, and companies could marginally change their drugs to extend the patent life by years and sell them as new treatments. The potential returns were very high and the development path would not need to be innovative. Factors that have brought an end to this era include legislation such as the 'Affordable Care Act' in the USA, stipulating new drugs significantly outperform available products to get reimbursed by medical insurance, and the increasing ease of obtaining approval for generic versions of drugs. Another reason for the lack of uptake of quantitative methods may be that many pharmaceutical leaders have traditionally based their decisions more on qualitative evidence.

In drug development, complex high-value decisions with lasting consequences must be made. These decisions are made by trial management teams in the context of uncertainty with data from many sources. One problem is cognitive bias; a lack of quantitative methods to support decision making often leads to poor decisions in complex situations, such as when decisions are made to solve a problem that can be solved more easily, rather than the one that should be solved.

This thesis aims to consider several processes in different areas of drug development and develop methods to aid quantitative decision making. By studying these methods, one may gain an appreciation of the complex situations and trade offs that are inherent in these complex high-value decisions.

Thesis organisation

Below, we summarise the chapters of this thesis.

In Chapter 1, we introduce the different settings in drug development considered in this thesis, and introduce the methods and techniques one may use to perform quantitative decision making. In particular, we introduce the concepts of Bayesian decision theory and the method of dynamic programming. These can be used in tandem to compute quantitative decision rules in the different settings in drug development.

Chapter 2 introduces adaptive design techniques which have been developed in the last few decades. Chapter 3 considers the value that these adaptive design techniques bring to a Phase II/III programme where Phase II has multiple treatments. A simulation study is performed to find the decision rules and assess the value of these adaptive design techniques.

Chapter 4 focuses on Phase II/III programmes where the treatments in Phase II are different doses of the same drug. In a similar way to Chapter 3, we look at the value that dose response modelling techniques can bring to a Phase II/III programme in this setting.

Chapter 5 considers the Phase II/III programme setting again but looks at the effect of having two confirmatory Phase III trials within the Phase II/III programme. We consider the best way to perform the programme in this case.

Chapter 6 considers the portfolio problem, which asks how one may best allocate a research and development budget to a portfolio of many drugs which are approaching Phase III. We formulate a statistical model for the portfolio problem, describe previous attempts to tackle it, and suggest a dynamic programming method approach. Using this approach, we consider different portfolio case studies to identify what one can learn from this problem.

Chapter 7 develops theory in order to construct optimal group sequential designs, which are optimal according to some general gain function. We motivate this approach, show how these designs can be computed, and analyse their properties.

1 Optimal Decisions in Drug Development

1.1 Introduction to Phase II/III programmes

Despite the cost of drug research and development increasing, clinical trial programmes in some therapeutic areas continuously have very high failure rates. A good trial design aims to try to find suitable treatments more efficiently, and discard unsuitable treatments more quickly. The use of more innovative statistical techniques has the potential to reduce failure rates by allowing the sponsor to make better use of data collected to inform decisions throughout the programme.

Whilst efficient statistical methods in individual phases of drug development have been studied extensively, relatively less work has been done on studying the entire programme of phases. Although useful, optimisation of each individual phase does not lead to a programme with optimal properties. However, designing an efficient programme over multiple phases is more difficult than designing a trial for a single phase.

In the drug development process, it is often the case that several doses or treatments show the potential to be safe and efficacious from pre-clinical and Phase I studies. Phase II may involve running proof of concept (Phase IIa) and/or dose finding (Phase IIb) trials. Proof of concept trials may be run with a criterion specifying whether to continue or not based on observed data. Dose finding trials may also be run to find the dose or treatment to take forward to the next stage. One or two Phase III confirmatory trials will then be performed to assess the efficacy of the chosen treatment or dose by conducting a frequentist hypothesis test. If the treatment is successful at this stage, the evidence will be submitted to regulatory bodies for approval.

In this thesis, we study the optimisation of programmes containing the Phase II and III aspects of the drug development process. In these programmes, one is required to be efficient in identifying efficacious doses or treatments, and to build evidence of the efficacy of the chosen dose or treatment such that there is sufficient evidence to submit to the regulatory bodies for marketing approval.

In Chapters 2 and 3 we consider the Phase II/III programme with multiple treatments in Phase II. Chapter 4 considers a similar problem but assumes the multiple treatments are doses of the same drug. In Chapter 5 we consider a Phase II/III programme with multiple Phase III trials.

1.1.1 Previous research

Research which considers optimising Phase II and III as a programme has been relatively recent, with previous research generally focusing on the optimisation of a study consisting of a single phase. In this section we review some of these approaches.

The approaches can be characterised by the following ingredients:

- The measure used to optimise the programme, such as expected net present value or probability of success (assurance).
- Assumptions about the distribution of the data. For example, the use of Gaussian, time to event, or discrete endpoints.
- Whether the purpose of Phase II is solely a proof-of-concept study, or involves some dose-finding or treatment selection routines with multiple treatments.

Antonijevic et al. (2010) compares different Phase II dose-selection strategies in terms of the expected net present value of the entire Phase II/III programme. The different Phase II dose-selection strategies included adaptive designs that allowed the treatment allocation randomisation to change based on the data collected, and adaptive analyses that allowed the method of analysis to be driven by the data. It was found using simulation studies that design-adaptive dose finding designs (such as Bayesian general adaptive dose allocation and the D-optimal response-adaptive approach) added the most value to the programme.

Jiang (2011) considers normal endpoints for a single treatment in a Bayesian approach. The probability of success is used as the measure by which to optimise the programme, and various optimal sample size and go/no-go decision rules are algebraically derived.

Patel et al. (2012) consider time to event endpoints for a range of doses entering Phase II. The expected net present value is used to make optimal decisions relating to the Phase II sample size, dose selection, and the sample size of Phase III. The paper also involves a novel method for obtaining posterior samples from the posterior distribution of parameters of dose response models. We look at this method in Chapter 3.

Marchenko et al. (2013) and the following paper Parke et al. (2017) also describe an approach using time to event endpoints. Multiple treatments are used in Phase II, and expected net present value is considered as a measure to optimise the Phase II design. In the latter paper, different adaptive Phase II and III designs are considered such as trials containing interim analyses, and group sequential methods. We consider this paper more thoroughly in Chapter 2.

Commercial software packages such as EAST (EAST-6 (2019)) have started to include programme level optimisation procedures as of 2019 showing the recent interest in this area.

1.2 Introduction to Phase III portfolios

Investing in drug development is a risky business. In order to mitigate the risk with a single drug or product asset, investor groups or large pharmaceutical companies may consider investing in a portfolio of drugs. One may define a portfolio as at least 3 drugs. Each individual drug may have a high potential of failure due to several reasons; failure in proof of concept trials, failure to progress to the next phase of development, failure in getting regulatory approval, or an inadequate sales forecast. Pooling investment into a portfolio of

drugs increases the chance of at least one success. Because potential revenues from marketing the drug far out-way development costs, only a small number of successes may be all that is necessary to return a profit on the investment.

For this reason, large pharmaceutical companies develop or acquire drugs with the intention of developing a portfolio. Decisions related to investment in candidate drugs in a portfolio are driven by the magnitude of risk to the investor and the palatability of the returns to the seller. Antonijevic (2014) notes that experience suggests that investments are abandoned not because of a flaw in the product or company, but because of the proposed return scheme.

While optimising the decision making of programmes in drug development is more desirable to optimising each phase of the programme separately, taking another step back to look at portfolios of several drugs may lead to an appreciation of the bigger picture. For example, budget commitments to a drug have to be made with the opportunity cost of less money being available for other drugs. On the other hand, if one sets aside funds for drugs in the future and they fail to progress, there may be delays in development of drugs one could have invested in sooner.

Decisions about investment in portfolios can be undertaken in a quantitative, value-driven way in order to maximise their value. Assessing the value of this portfolio depends upon the financial aspects of each drug and upon the portfolio decision making strategy. Budget limits will be set at portfolio levels which makes any decisions interrelated. Given budget constraints, not all planned programmes can be executed which focuses the problem on potential returns. Further complications are that the decisions involve the number of patients recruited for the programmes and there is uncertainty about if potential drugs will have technical failures before becoming available to invest in.

In industry it is common to fix the level of power of Phase III trials at a predetermined level not linked to the financial value of a drug. It may be the case that when looking at the larger portfolio picture, more value is obtained by choosing the power based upon both the drug's financial value and portfolio considerations.

In Chapter 6, we consider the portfolio problem, and construct a method for finding the optimal decision rules under a statistical model.

1.2.1 Previous research

Previous attempts at modelling a portfolio of drugs as a mathematical model that has an optimal development strategy have been made.

Many of these approaches have come from operational research and use integer programming (IP) with some kind of budget constraints. In particular, some either extend the formulation to stochastic programming (Gatica et al. (2003), Colvin and Maravelias (2009), Jacob and Kwak (2003), Colvin and Maravelias (2008)), or use simulation models (Varma et al. (2008), Rogers et al. (2002), Blau et al. (2003), Solo et al. (2004), Solak et al. (2010)). Most approaches use the expected net present value (eNPV) as a measure of return with different ways of including risk whilst others use real option theory.

These approaches have generally not considered the choice of design for each programme in the portfolio. However the choice of design is a key decision variable influencing the probability of success of the Phase III trials of each drug. An approach which does consider the choice of design and we closely follow in this thesis is the work of Patel and Ankolekar

et al. (Patel and Ankolekar (2007) and Patel et al. (2013)). They use a Bayesian two-point prior at the design stage to calculate the probability of success and eNPV and help determine the choice of design for the Phase III trials of each drug in the portfolio. The problem is formulated as a stochastic integer programming (SIP) problem and an SIP solver is used to derive the optimal decision rules.

1.3 Bayesian decision theory

Decision theory is a study of principles and algorithms with the aim of making correct decisions. That is, decisions that allow one to achieve better outcomes with respect to one's goals. Any action that one takes may be considered as a decision under uncertainty. The way decisions are made must have some underlying mechanism and decision theory is the study of how to make good decisions.

Bayesian decision theory is a decision theory that is informed using Bayesian probability. It is a decision making mechanism that attempts to quantify the trade off between different decisions using probabilities and costs.

Any kind of probability distribution or degree of belief about a random variable may represent a prior distribution and Bayesian theory provides us with a method to obtain posterior distributions representing the current belief about a random variable given observed data. A core concept in Bayesian decision theory is the use of Bayesian probabilities to estimate the expected value of each action, and the updating of these expectations based on new information.

Berger (2013) is a popular reference on Bayesian decision theory, giving the underlying theory with examples in different areas. The links between decision analysis and Bayesian ideas are explored. Pham-Gia (1997) also explores these topics, with arguments that the sample size for an experiment can be chosen based on Bayesian decision theory.

Bayesian decision theory has been used in previous research in application to trials in different phases of drug development. Stallard (1998) uses it to derive optimal group sequential designs for Phase II for binary outcomes. In a similar way, Gittins and Pezeshk (2000) derives the optimal sample size for a Phase III trial using the posterior distribution of the treatment effect. Senn (2008) and O'Hagan et al. (2005) both show how Bayesian decision theory can be applied in a grander context, in particular for options of a clinical development plan or project prioritisation in a portfolio.

1.3.1 Bayes' optimal decision rules

Single decision making

In this section, we define some notation and derive Bayes' optimal decision rule for a single decision.

Let the random variable of the underlying state of nature be denoted by $\boldsymbol{\Theta}$ with the set of all states denoted by $\boldsymbol{\Omega_\theta}$, and with each element denoted by $\boldsymbol{\theta}$. Suppose there is a prior distribution $\pi(\boldsymbol{\theta})$ for the state of nature. Denote the random variable $\boldsymbol{X}$ as the data with the set of possible observed data as $\boldsymbol{\Omega_x}$ with elements $\boldsymbol{x}$. The probability density function of $\boldsymbol{X}$ can be denoted as $f(\boldsymbol{x};\boldsymbol{\theta})$, where $\boldsymbol{\theta}$ is a parameter in the density function.

Denote possible actions one may take as $\boldsymbol{\Omega_a}$ with elements a, and let a decision rule d be a function of data to actions $d : \boldsymbol{\Omega_x} \to \boldsymbol{\Omega_a}$. Finally let the gain function $\mathcal{G}$ be a function of actions and states of nature to the real numbers, $\mathcal{G} : \boldsymbol{\Omega_a} \times \boldsymbol{\Omega_\theta} \to \mathbb{R}$, such that $\mathcal{G}(a, \boldsymbol{\theta})$ is the gain incurred when one takes action a when the state of nature is $\boldsymbol{\theta}$.

Suppose the likelihood of the data given $\boldsymbol{\theta}$ is denoted by $f_{\boldsymbol{X}|\boldsymbol{\theta}}(\boldsymbol{x}|\boldsymbol{\theta})$, and denote the probability density function of the posterior distribution of $\boldsymbol{\theta}$ given data $\boldsymbol{x}$ as $\pi_{\boldsymbol{\Theta}|\boldsymbol{X}}(\boldsymbol{\theta}|\boldsymbol{x})$.

Define decision rule d to maximise the expected value of the gain function, $\mathbb{E}\left[\mathcal{G}(d(\boldsymbol{X}), \boldsymbol{\Theta})\right]$, and note that

$$\begin{aligned}
\mathbb{E}\left[\mathcal{G}(d(\boldsymbol{X}), \boldsymbol{\Theta})\right] &= \int_{\boldsymbol{\Omega_\theta}} \pi(\boldsymbol{\theta}) \int_{\boldsymbol{\Omega_x}} f_{\boldsymbol{X}|\boldsymbol{\theta}}(\boldsymbol{x}|\boldsymbol{\theta})\ \mathcal{G}(d(\boldsymbol{x}), \boldsymbol{\theta})\ d\boldsymbol{x}\ d\boldsymbol{\theta} \\
&= \int_{\boldsymbol{\Omega_x}} \int_{\boldsymbol{\Omega_\theta}} \pi(\boldsymbol{\theta})\ f_{\boldsymbol{X}|\boldsymbol{\theta}}(\boldsymbol{x}|\boldsymbol{\theta})\ \mathcal{G}(d(\boldsymbol{x}), \boldsymbol{\theta})\ d\boldsymbol{\theta}\ d\boldsymbol{x} \\
&= \int_{\boldsymbol{\Omega_x}} f_{\boldsymbol{X}}(\boldsymbol{x}) \left[\int_{\boldsymbol{\Omega_\theta}} \pi_{\boldsymbol{\Theta}|\boldsymbol{X}}(\boldsymbol{\theta}|\boldsymbol{x})\ \mathcal{G}(d(\boldsymbol{x}), \boldsymbol{\theta})\ d\boldsymbol{\theta} \right] d\boldsymbol{x}.
\end{aligned} \tag{1.1}$$

Therefore decision rule d may be written as

$$d(\boldsymbol{x}) = \underset{a \in \boldsymbol{\Omega_a}}{\operatorname{argmax}} \int_{\boldsymbol{\Omega_\theta}} \pi_{\boldsymbol{\Theta}|\boldsymbol{X}}(\boldsymbol{\theta}|\boldsymbol{x})\ \mathcal{G}(a, \boldsymbol{\theta})\ d\boldsymbol{\theta}, \tag{1.2}$$

which is named as Bayes' decision rule. Intuitively, Bayes decision rule chooses the action which maximises the expected value of the gain function, computed in the Bayesian sense given the information observed so far.

Sequential decision making

In our setting, states of nature can refer to the unknown treatment effect(s) of the treatment(s) under consideration in the programme. Observed data represents the data from clinical trials with control and treatment arms. Actions taken in a programme may be related to the choice of the future design of the programme, such as the number of patients to test, the treatment to take forward, or whether to continue at all. The gain function represents the value of different realisations of the programme to the sponsor. This may depend upon whether a treatment was granted regulatory approval or not, how long the programme took, and the number of patients that were required to be tested.

In a clinical trial programme, often one has many decision points which are chronologically sequential. We adapt the single decision making mechanism in order to find Bayes' decision rule in this case.

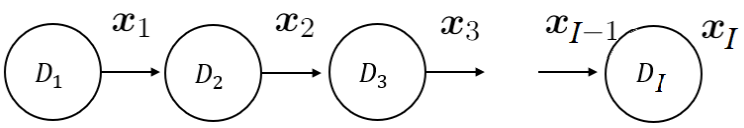

Figure 1-1: A schematic of a sequential decision making process.

Let there be I decision points in our sequential decision problem. At decision point $i \in \{1, ..., I\}$, one chooses an action $a_i \in \boldsymbol{\Omega_{a_i}}$, which may affect the distribution of the data collected after this decision point. After decision point $i \in \{1, ..., I-1\}$ is made, one observes data $\boldsymbol{x}_i$.

The gain function $\mathcal{G}((d_1, ..., d_I), (\boldsymbol{x}_1, ..., \boldsymbol{x}_I), \theta)$ is generalised to take account of all the data in the sequence as well as all of the decision rules.

The problem then becomes one of finding decision rules $d_1, ..., d_I$ that maximise

$$\mathbb{E}(\mathcal{G}((d_1, ..., d_I), (\boldsymbol{X}_1, ..., \boldsymbol{X}_I), \Theta)). \tag{1.3}$$

By integrating over the future data and state of nature, similarly to the single decision case, we can derive Bayes' decision rules for a sequential decision making problem. In Appendix 1.A, we show how this may be done algebraically. Intuitively, Bayes' decision rule at each stage is the one that, given current information (that is, all previous data), maximises the expected value of the gain function given future decision points follow Bayes' decision rule. This may be found by integrating over the posterior distribution of the state of nature given previously observed data and then integrating over the distribution of future data.

Integrating over future data of a decision point before the last stage (that is, when $i < I$) involves knowing the Bayes decision rule at the next stage (that is, stage $i + 1$). If the problem is simple enough, one may compute the Bayes decision rule at the next stage directly. However, this link between each successive decision rule means an iterative method such as dynamic programming can be naturally used to calculate Bayes decision stage by stage. This may be more efficient for more complex problems. In Section 1.4.1, we explore how this can be done.

Application: Phase II/III programmes (Chapters 3,4,5)

In this application we have two decision points in the Phase II/III programme. In particular, the choice of Phase II design, and the choice of Phase III design. As there are only two decision points, one may compute Bayes decision rule directly at each decision point, by integrating over the treatment effect and future data.

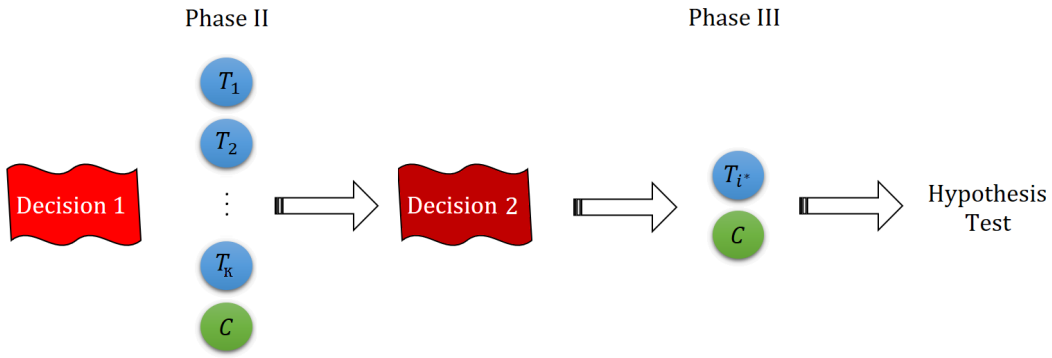

Figure 1-2: A schematic showing the dynamic programming method applied to a Phase II/III programme with multiple treatments (denoted T_1 to T_K) and control (denoted C) in Phase II. Decision 1 refers to the decision point before Phase II which involves the choice of Phase II design, and Decision 2 refers to the decision point after Phase II and before Phase III which involves the choice of treatment to use in Phase III (denoted i^*) and the Phase III design. A frequentist hypothesis test is then performed to decide whether the treatment can be marketed.

1.4 Dynamic programming

Dynamic programming is a mathematical optimisation method formulated by Bellman in the 50s (Bellman (1957)). The method involves simplifying a complicated problem by breaking it down into smaller sub-problems and solving them in a recursive manner. We illustrate how dynamic programming can be used to find Bayes' decisions in Equation 1.3 in different situations.

1.4.1 Dynamic programming with Bayesian decision theory

As in the sequential decision making in Section 1.3.1, there are stages in the process which we denote by $i = 1, ..., I$. These may be decision points during a programme, portfolio, or interim analyses in a trial. At any decision point i, one may be at a particular state s, with the set of all possible values s can take being denoted by S_i. The aim is to know Bayes' optimal decision and corresponding expected value of the gain function (which we refer to as the *optimal decision* and the *expected gain* for brevity) at any state and decision point.

The method of dynamic programming requires a dynamic programming *central equation* to link the expected gain of a particular action $a_i \in \mathbf{\Omega}_{a_i}$ at a state s at drug i in terms of the expected gain of the optimal decisions at different states in S_{i+1} at drug $i+1$. The form this equation takes depends upon the application, describes the different states one may move to at the following stage, and comes from the innate structure inherent in the problem.

Once these are defined, one will generally proceed with the following dynamic programming algorithm:

`DP_func`

- Compute the optimal decision and corresponding expected gain for any state $s \in S_I$ at the final stage I.
- For each $i = I - 1, ..., 1$:
  - For each state $s \in S_i$ at stage i, using the dynamic programming *central equation* find the action which maximises the expected gain (that is, the optimal decision) and store this optimal decision and corresponding expected gain.
- Return the optimal decision rules and corresponding expected gain for each state and stage.

The output of this algorithm contains the optimal decision rules at each stage. The corresponding expected gain of the optimal decision at the initial state at stage 1 represents the expected value of the gain function at the beginning of the process. This may be thought of as the *value* of the process.

Application: Phase III portfolios (Chapter 6)

In this application the stages may be times at which different drugs are becoming available for Phase III trials with decision points as each drug becomes available with the decisions some choice of design of the Phase III trial for each drug. There may be a large budget to spend on all the drugs within the portfolio, and the decision rules stipulate how the budget is allocated to each drug. We require optimal decision rules giving the optimal allocation

of budget given the current state, such as the portfolio budget remaining. The dynamic programming method finds the optimal decision rules for the last drug, and then recursively uses the *central equation* to find the optimal decision rules for drugs $I-1$, $I-2$,...,1. We illustrate this in the schematic below.

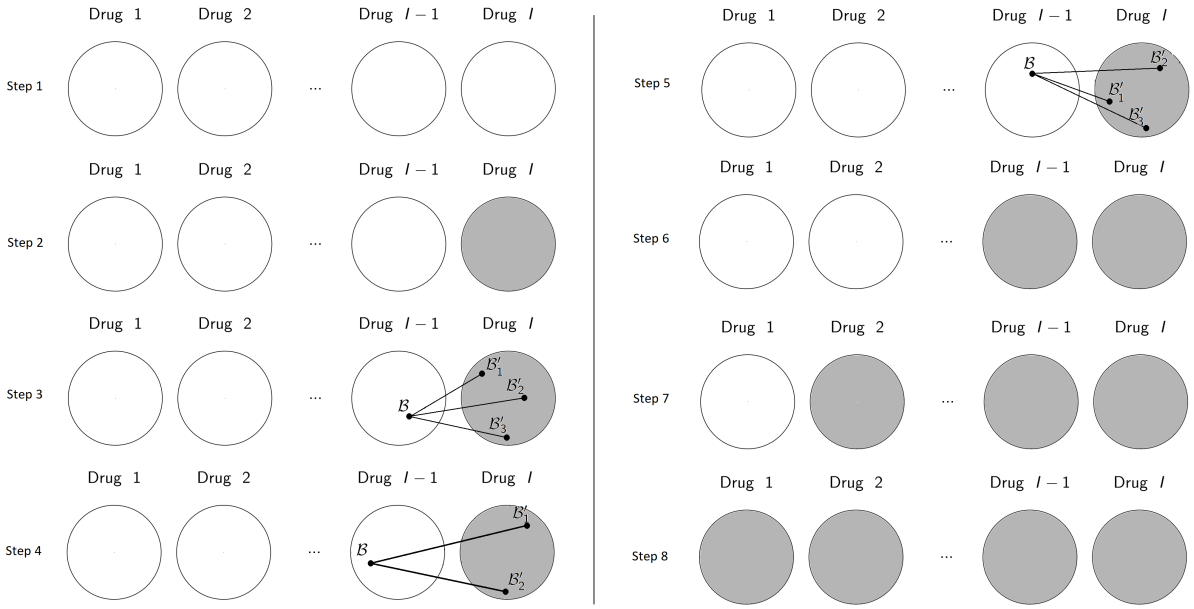

Figure 1-3: A schematic showing the dynamic programming method applied to a portfolio. The white circles refer to the state space of a drug (for example, the total remaining portfolio budget $\mathcal{B}$) with the grey circles representing the state space where the optimal decision rule has been calculated for every state in that state space. The rows indicate how the algorithm proceeds. In Steps 1-2, the optimal decision rules are found for every state space at the last drug. Steps 3-6 illustrate the use of the *central equation* to calculate the optimal decision rule for drug $I-1$ using the saved optimal decision rules from final drug I as part of the calculation. That is, given one is at state $\mathcal{B}$ at drug $I-1$, the *central equation* requires the optimal decision at different $\mathcal{B}'$ at drug I. This process is repeated iteratively in steps 6-8 until optimal decisions have been found for every state at every drug.

Application: Group sequential designs (Chapter 7)

Another use of dynamic programming is the derivation of optimal group sequential designs under some error constraints and an optimality criterion. This frequentist problem may be reformulated as a Bayesian decision theory problem that is solved with dynamic programming. The dynamic programming method involves finding the optimal critical values for the group sequential design at the final stage, and working backwards stage by stage, finding the optimal critical values each time until the first stage, under some costs of making an incorrect decision. The original problem of finding the optimal design under the given constraints can then be solved by using the Lagrangian multiplier method of performing a search over costs of making an incorrect decision until the error constraints of the original problem are met.

The stages are the interim analyses $k = 1, ..., 5$ of the group sequential design with acceptance and rejection boundaries a_k and b_k.

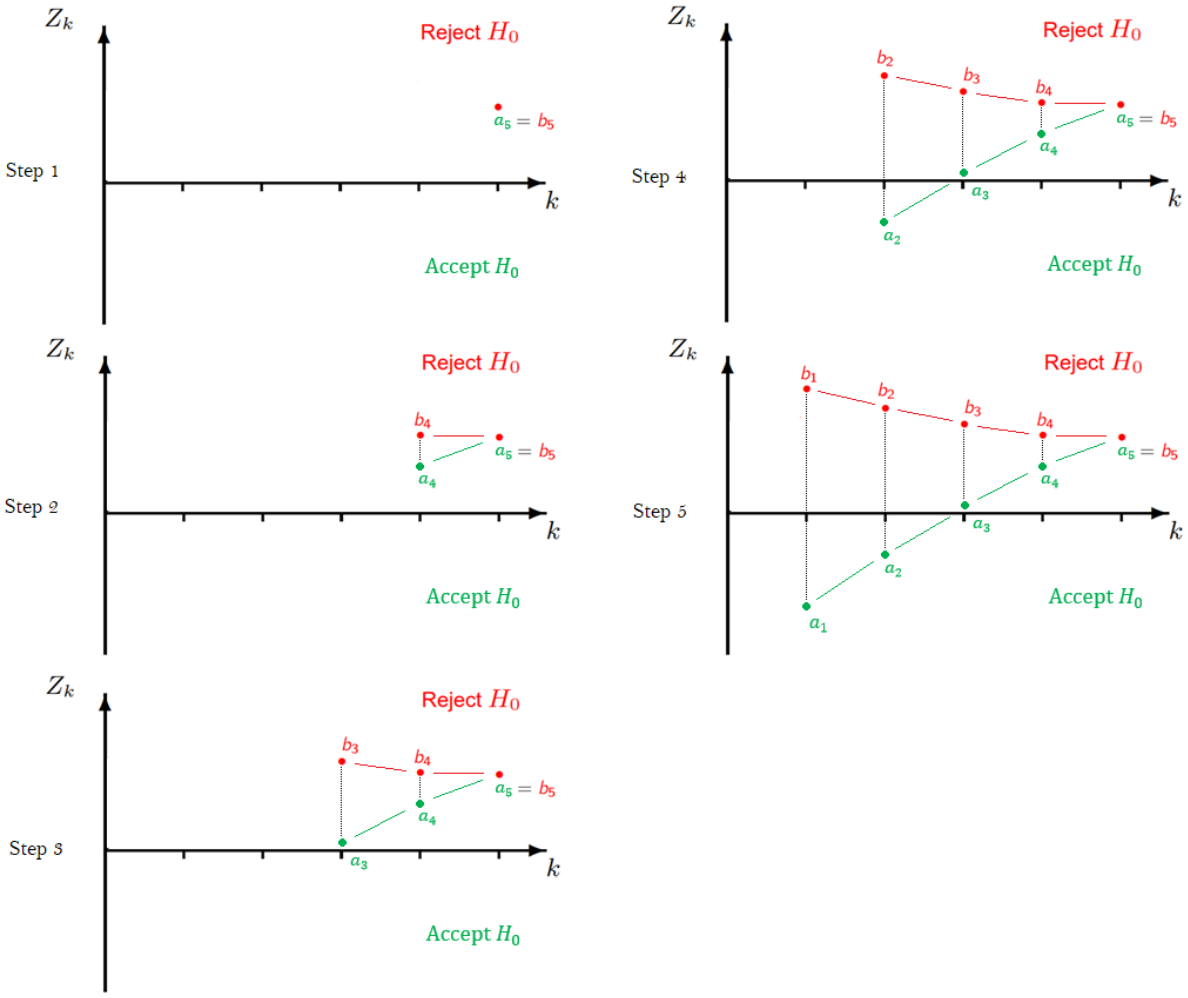

Figure 1-4: A schematic showing the dynamic programming method applied to a group sequential design. The steps indicate how the algorithm proceeds by finding the optimal boundaries for each interim analysis starting from the final analysis and working backwards.

1.5 Types of gain functions

In Bayesian decision theory, one requires a gain function to be specified, and decisions are taken to maximise the expected value of this gain function. How this gain function is defined depends upon the value one allocates to different realisations of the process.

In this thesis, we generally use gain functions which measure the financial value of a particular realisation to the investigator in terms of net present value. Alternatives include the return ratio, for example studied in Chen and Beckman (2014). In this section, we outline the net present value concepts that are used to construct gain functions.

1.5.1 Net present value

During drug development, resources are invested up front with the hope of recovering costs and acquiring large revenue streams once the drug becomes a commercial product. Net present value (NPV) has been used in many industries as a financial measure of returns, representing in this context the difference between the present value of any future revenue streams and the amount of investment. The revenue streams are highly dependent upon

whether drugs are approved or not, which is not known until the end of the development process. Therefore a common measure to use under this uncertainty is the expected net present value (eNPV) which represents the NPV weighted by the development risks.

The advantage of using the eNPV is that it naturally accommodates optimisation. For example, changing a trial design may increase the power of the test, but this may come at the expense of recruiting extra subjects. The power increases with the number of subjects, whilst the eNPV balances the increase in power with the monetary and time cost of treating extra patients.

The eNPV measure fits harmoniously with Bayesian decision theory. The gain function represents the NPV which, at the start of the programme, includes large sources of variability due to technical risks of success and failure of the development process, with the eNPV relating to the expected value of the development process, which is required when making Bayes decisions.

There are several criticisms of eNPV. For many drug development programmes, the cost of the programme is a small fraction of the realised revenues. Therefore the costs of a programme can become much less important than relatively small changes in the revenue. However, a sponsor may have a budget to spend on research and development across a whole portfolio of programmes. If a programme takes too many resources, there is an opportunity cost where other studies which may have been productive cannot now be funded. To attempt to mitigate this problem, one can consider the portfolio problem as a whole.

The NPV gain function must quantify the trade offs between advantages and disadvantages of different decisions in the drug development process. To do this, we require the following features:

- Large gain when a treatment is deemed successful in the programme representing the revenue realised from a treatment which has regulatory approval. Time considerations may also be incorporated.
- Development costs from Phase II and Phase III dependent on the number of patients required for each phase.
- Safety penalties in situations where there is uncertainty about the suitability of a drug due to safety or side effect reasons.
- Gains and losses in the future may be discounted to represent their true current values.

In the sections below, we outline two forms of gain function we use during this thesis.

A simple gain function

The first gain function we consider is of a simple form that aims to simply quantify the trade off between a larger sample size and power and increased costs of development. Consider a drug development programme in which patients are tested in two distinct phases, Phase II and Phase III.

One defines constant G and function ζ such that $G\zeta(\theta_i)$ is the value to the sponsor of treatment i being successful in the programme, given the true treatment effect was θ_i. Positive real numbers γ_1, γ_2 are defined as the cost of treating a patient in Phase II and III respectively. Denote N_1 and N_2 as the total number of patients in Phase II and III respectively.

The gain function is hence defined as

$$\mathcal{G} := G\ \zeta(\theta_i)\ \mathbb{1}_{\{\text{Drug } i \text{ is successful}\}} - \gamma_1 N_1 - \gamma_2 N_2. \tag{1.4}$$

A financial model

The second gain function we consider is more detailed and aims to more accurately model the different financial aspects of the decision making process.

We do not define the exact form of a financial model here as it will contain many parameters relevant to the context in drug development, but we describe the different features it may contain.

A drug undergoing a Phase II or III clinical trial will have a fixed cost to set up the trial, as well as a cost per patient recruited. The trial will take a time proportional to the time taken to recruit all the patients, plus the time taken to observe responses from the last recruited patient.

Assuming a programme is successful, if one wishes to market the drug there will be a cost and a time period involved in setting up the marketing. Once this marketing has been set up, one will realise a revenue from marketing the drug until the patent expires.

We use a financial model gain function in Chapters 3, 5, and 6. The calculations in the financial model are highly dependent upon the drug development process studied, so we define the model fully in each of the applications in these chapters.

1.6 Computational approaches

In many chapters of this thesis, we require computational techniques to evaluate integrals arising from decision rules. In this section, we summarise some of these methods.

1.6.1 Numerical Integration Techniques

Numerical integration techniques can be used to efficiently calculate low dimensional integrals. Below, we illustrate a method to evaluate a common integral in this thesis.

A 1D numerical integration routine

Consider

$$\int_{\mathbb{R}} f(x)\pi(x)dx, \tag{1.5}$$

where π is the density function of a normal distribution. In this section, we provide a method for solving this integral, which breaks up the range of integration into a set of intervals- dense around the peak of $\pi(x)$, and logarithmically spaced out in the tails.

We suppose that f is a smooth function on the entire domain, with the possible exception of a finite number of discontinuities. If there are discontinuities, the location of these must be known a-priori.

We take the approach of Chapter 19 in Jennison and Turnbull (2000) where the integration points are placed more densely near the mean of the normal distribution and logarithmically placed away from the mean. The composite version of Simpson's rule is then applied to intervals within these integration points.

Denote r as a parameter controlling the number of integration points. Let π be the probability density function of the normal distribution $N(\mu, \sigma^2)$.

Creation of initial integration points x

The initial integration points $x_1, ..., x_{6r-1}$ are defined by

$$x_i = \begin{cases} \mu + \sigma(-3 - 4\log(r/i)) & i = 1, ..., r-1, \\ \mu + \sigma(-3 + 3(i-r)/2r) & i = r, ..., 5r, \\ \mu + \sigma(3 + 4\log(r/(6r-i))) & i = 5r+1, ..., 6r-1, \end{cases} \tag{1.6}$$

The function and corresponding density is evaluated at each initial integration point to obtain

$$f(x_1)\pi(x_1), f(x_2)\pi(x_2), ..., f(x_{6r-1})\pi(x_{6r-1}). \tag{1.7}$$

Adding in adaptive integration points

New points may be added at this stage at any point on the real line. Suppose in particular there is a discontinuity in f. We input integration points on either side of the discontinuity. Suppose the discontinuity occurs at x^*. Create new points $x' = x^* - \epsilon$ and $x'' = x^* + \epsilon$ for some small $\epsilon > 0$. Compute the corresponding function evaluations and insert into the integration point list, shifting the indices as appropriate, so that there are 2 extra integration points.

Filling in the remaining integration points

Let m be the number of integration points created so far. Then let $N = 2m - 1$.

Compute the full set of integration points $z_1, ..., z_N$ by setting $z_i = x_{(i+1)/2}$ for $i = 1, 3, ..., N$, and $z_i = (z_{i-1} + z_{i+1})/2$ for $i = 2, ..., N-1$.

Compute the function evaluations for the integration points which have not yet been computed, $f(z_1)\pi(z_1), ..., f(z_N)\pi(z_N)$.

Using the composite Simpsons rule to evaluate the integral

The idea is that one computes the integral between two grid points with odd indices z_{i-1} and z_{i+1} as

$$\frac{d}{6} f(z_{i-1})\pi(z_{i-1}) + \frac{4d}{6} f(z_i)\pi(z_i) + \frac{d}{6} f(z_{i+1})\pi(z_{i+1}). \tag{1.8}$$

Therefore the weights corresponding to the whole integration line are

$$w_i = \begin{cases} \frac{1}{6}(z_3 - z_1) & i = 1 \\ \frac{1}{6}(z_{i+2} - z_{i-2}) & i = 3, 5, ..., N-2 \\ \frac{4}{6}(z_{i+1} - z_{i-1}) & i = 2, 4, ..., N-1 \\ \frac{1}{6}(z_N - z_{N-2}) & i = N \end{cases} \tag{1.9}$$

which give us the following approximation for the integral,

$$\int_{\mathbb{R}} f(x)\pi(x)dx \approx \sum_{i=1}^{N} w_i f(z_i)\pi(z_i) \tag{1.10}$$

Equation 1.10 therefore allows us to integrate equations of the form of Equation 1.5. Simpson's rule has error of order $O(N^{-4})$.

1.6.2 Monte Carlo

Another method for evaluating integrals is to use Monte Carlo simulation (Metropolis and Ulam (1949)). This is particularly useful for higher dimension integrals where using numerical integration techniques becomes computationally expensive.

If

$$I = \int_{\Omega} f(\boldsymbol{x})\pi_X(\boldsymbol{x})d\boldsymbol{x} \tag{1.11}$$

with $\Omega \subseteq \mathbb{R}^{|\boldsymbol{x}|}$ needs to be evaluated, the Monte Carlo approach is to sample points from the random variable X with probability density function $\pi_X(\boldsymbol{x})$. Let

$$\boldsymbol{X}_1, ..., \boldsymbol{X}_N \overset{\text{iid}}{\sim} \pi_X, \tag{1.12}$$

with observed values $\boldsymbol{x}_1, ..., \boldsymbol{x}_N$. Then we use approximation

$$I \approx \frac{1}{N}\sum_{i=1}^{N} f(\boldsymbol{x}_i). \tag{1.13}$$

The Monte Carlo method has error $O(N^{-1/2})$ so is slower to converge than using numerical integration. Below, we list two ways the method can be made more efficient.

Use of splines

Consider a function $f(\boldsymbol{x})$ which is computationally expensive to compute. Suppose we wish to compute I from Equation 1.11 with the Monte Carlo approximation in Equation 1.13.

One wishes to avoid unnecessary evaluations of this function in the Monte Carlo routine. However the error of the Monte Carlo method means a large number of simulations are needed. One solution would be to use only a small number of Monte Carlo simulations, but this would mean the Monte Carlo estimate has a larger amount of uncertainty attached associated with it. Below, we outline another solution based upon the interpolation of splines. This is our own method.

Suppose that $\boldsymbol{x}$ is one or two dimensional.

- Perform the Monte Carlo integration for $N_{initial}$ ($<< N$) initial runs, saving the value of $\boldsymbol{x}$ each time in vector $(\boldsymbol{x}_1, ..., \boldsymbol{x}_{N_{\text{initial}}})$ and the values f takes in vector $(f(\boldsymbol{x}_1), ..., f(\boldsymbol{x}_{N_{\text{initial}}}))$.
- Fit a 1-dimensional or 2-dimensional spline with covariates $(\boldsymbol{x}_1, ..., \boldsymbol{x}_{N_{\text{initial}}})$ and response variables $(f(\boldsymbol{x}_1), ..., f(\boldsymbol{x}_{N_{\text{initial}}}))$.
- Denote by $f^*(\boldsymbol{x})$ a function which estimates the value of $f(\boldsymbol{x})$ based on interpolating using the fitted spline without calculating $f(\boldsymbol{x})$ explicitly.

- Perform the Monte Carlo integration for a further $N - N_{initial}$ runs, using f^* instead of f.
- Return the Monte Carlo estimate over the full N Monte Carlo simulations.

One must ensure $N_{initial}$ is large enough such that the probability space of the covariate in the spline is adequately explored, and the spline smoothing parameter is appropriately defined to ensure the spline follows the relationship between the covariate and response adequately.

In 1-dimension, one may use cubic splines (De Boor (1978)) and in 2-dimensions, thin plate splines (Bookstein (1989)).

Coupling

We describe another of our own methods for reducing the uncertainty associated with an estimator. Suppose we wish to compute $I_1 - I_2$ where

$$\begin{aligned} I_1 &= \int_X f(\boldsymbol{x}; m_1)\pi(\boldsymbol{x}; m_1)d\boldsymbol{x}, \text{ and} \\ I_2 &= \int_X f(\boldsymbol{x}, m_2)\pi(\boldsymbol{x}; m_2)d\boldsymbol{x}, \end{aligned} \tag{1.14}$$

where f is a function of vector $\boldsymbol{x}$ and integer m, and the probability density function π is Gaussian with mean $\boldsymbol{\theta}_m$ and covariance matrix Σ_m. One may compute Monte Carlo estimates I_1^{mc} and I_2^{mc} of each integral.

The coupling procedure introduces correlation between the Monte Carlo estimators of each integral in Equation 1.14, reducing the variance of the difference between the two estimators. If there is more correlation between the estimators I_1^{mc} and I_2^{mc}, then the variance of the estimate $I_1^{mc} - I_2^{mc}$ of $I_1 - I_2$,

$$\text{var}(I_1^{mc} - I_2^{mc}) = \text{var}(I_1^{mc}) + \text{var}(I_2^{mc}) - 2\sqrt{\text{var}(I_1^{mc})\text{var}(I_2^{mc})}\text{corr}(I_1^{mc}, I_2^{mc}),$$

decreases.

Let $\boldsymbol{x}_1^{(1)}, ..., \boldsymbol{x}_N^{(1)}$ and $\boldsymbol{x}_1^{(2)}, ..., \boldsymbol{x}_N^{(2)}$ be the simulated values of $\boldsymbol{x}$. Suppose that Σ_m may be written as $\Sigma_m = \Lambda_m \Lambda_m^T$. This decomposition of the variance matrix is possible if it is positive definite (the case unless one random variable is an exact linear combination of others).

Instead of drawing the data independently, we propose coupling the simulated data as follows,

$$\begin{aligned} \boldsymbol{x}_i^{(1)} &= \boldsymbol{\theta}_{m_1} + \Lambda_{m_1}\boldsymbol{z}_i, \text{ and} \\ \boldsymbol{x}_i^{(2)} &= \boldsymbol{\theta}_{m_2} + \Lambda_{m_2}\boldsymbol{z}_i, \end{aligned} \tag{1.15}$$

where

$$\boldsymbol{z}_i \overset{\text{iid}}{\sim} N(0, I). \tag{1.16}$$

This introduces correlation between I_1^{mc} and I_2^{mc}. Suppose one wishes to find the choice of parameter m which maximises the expected value of function f, when f depends upon random data $\boldsymbol{x}$. As one calculates the expected value of f for different parameters, using this method will reduce the number of Monte Carlo simulations required to deduce the maximising parameter. This technique is used in Chapter 2 when studying Phase II/III programmes.

Section 1 Appendices

1.A Sequential Bayes' decision rule

We derive Bayes' decision rules for the sequential decision making problem using techniques analogous to the single decision problem. We require decision rules $d_1, ..., d_I$ such that the following expression is maximised:

$$\begin{aligned}
&\mathbb{E}(\mathcal{G}((d_1, ..., d_I), (\boldsymbol{X}_1, ..., \boldsymbol{X}_I), \Theta)) \\
&= \int_{\boldsymbol{\Omega_\theta}} \int_{\boldsymbol{\Omega x_1}} ... \int_{\boldsymbol{\Omega x_I}} \mathcal{G}((d_1, ..., d_I), (\boldsymbol{x}_1, ..., \boldsymbol{x}_I), \boldsymbol{\theta})\ \pi(\boldsymbol{\theta})\ f_{\boldsymbol{X}_1|\theta}(\boldsymbol{x}_1|\boldsymbol{\theta}) \\
&\quad \times f_{\boldsymbol{X}_2|\boldsymbol{\theta},\boldsymbol{X}_1}(\boldsymbol{x}_2|\boldsymbol{\theta}, \boldsymbol{x}_1)...f_{\boldsymbol{X}_I|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_{I-1}}(\boldsymbol{x}_I|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_{I-1})\ d\boldsymbol{x}_I, ..., d\boldsymbol{x}_1\ d\boldsymbol{\theta} \\
&= \int_{\boldsymbol{\Omega_\theta}} \int_{\boldsymbol{\Omega x_1}} ... \int_{\boldsymbol{\Omega x_I}} \mathcal{G}((d_1, ..., d_I), (\boldsymbol{x}_1, ..., \boldsymbol{x}_I), \boldsymbol{\theta})\ \pi_{\boldsymbol{\Theta}|\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{\theta}|\boldsymbol{x}_1, ..., \boldsymbol{x}_i)\ f_{\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{x}_1, ..., \boldsymbol{x}_i) \\
&\quad \times f_{\boldsymbol{X}_{i+1}|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{x}_{i+1}|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_i)...f_{\boldsymbol{X}_I|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_{I-1}}(\boldsymbol{x}_I|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_{I-1})\ d\boldsymbol{x}_I, ..., d\boldsymbol{x}_1\ d\boldsymbol{\theta} \\
&= \int_{\boldsymbol{\Omega x_1}} ... \int_{\boldsymbol{\Omega x_i}} f_{\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{x}_1, ..., \boldsymbol{x}_i) \int_{\boldsymbol{\Omega_\theta}} \pi_{\boldsymbol{\Theta}|\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{\theta}|\boldsymbol{x}_1, ..., \boldsymbol{x}_i) \int_{\boldsymbol{\Omega}_{\boldsymbol{x}_{i+1}}} ... \int_{\boldsymbol{\Omega}_{\boldsymbol{x}_{N_D}}} \\
&\quad \times \mathcal{G}((d_1, ..., d_I), (\boldsymbol{x}_1, ..., \boldsymbol{x}_I), \boldsymbol{\theta})\ f_{\boldsymbol{X}_{i+1}|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{x}_{i+1}|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_i)... \\
&\quad \times f_{\boldsymbol{X}_I|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_{I-1}}(\boldsymbol{x}_I|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_{I-1})\ d\boldsymbol{x}_I, ..., d\boldsymbol{x}_{i+1}\ d\boldsymbol{\theta}\ d\boldsymbol{x}_i, ..., d\boldsymbol{x}_1,
\end{aligned} \tag{1.17}$$

where Bayes' theorem is used to obtain the last expression. Note that $\pi_{\boldsymbol{\Theta}|\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{\theta}|\boldsymbol{x}_1, ..., \boldsymbol{x}_i)$ denotes the posterior distribution of $\boldsymbol{\theta}$ given observed data $(\boldsymbol{X}_1, ..., \boldsymbol{X}_i) = (\boldsymbol{x}_1, ..., \boldsymbol{x}_i)$ for $i = 1, ..., I$ and $f_{\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{x}_1, ..., \boldsymbol{x}_i)$ is the marginal probability density function for the data for $i = 1, ..., I$.

Therefore we choose d_i such that

$$\begin{aligned}
&\int_{\boldsymbol{\Omega_\theta}} \pi_{\boldsymbol{\Theta}|\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{\theta}|\boldsymbol{x}_1, ..., \boldsymbol{x}_i) \int_{\boldsymbol{\Omega}_{\boldsymbol{x}_{i+1}}} ... \int_{\boldsymbol{\Omega}_{\boldsymbol{x}_{N_D}}} \\
&\mathcal{G}((d_1, ..., d_I), (\boldsymbol{x}_1, ..., \boldsymbol{x}_I), \boldsymbol{\theta})\ f_{\boldsymbol{X}_{i+1}|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{x}_{i+1}|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_i)... \\
&f_{\boldsymbol{X}_I|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_{I-1}}(\boldsymbol{x}_I|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_{I-1})\ d\boldsymbol{x}_I, ..., d\boldsymbol{x}_{i+1}\ d\boldsymbol{\theta} \\
&= \int_{\boldsymbol{\Omega_\theta}} \pi_{\boldsymbol{\Theta}|\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{\theta}|\boldsymbol{x}_1, ..., \boldsymbol{x}_i)\ \mathbb{E}\left[\mathcal{G}((d_1, ..., d_I), (\boldsymbol{x}_1, ..., \boldsymbol{x}_i, \boldsymbol{X}_{i+1}, ..., \boldsymbol{X}_I), \boldsymbol{\theta})\right]\ d\boldsymbol{\theta}
\end{aligned} \tag{1.18}$$

is maximised, where

$$\begin{aligned}
\mathbb{E}\left[\mathcal{G}((d_1, ..., d_I), (\boldsymbol{x}_1, ..., \boldsymbol{x}_i, \boldsymbol{X}_{i+1}, ..., \boldsymbol{X}_I), \boldsymbol{\theta}\right) := \int_{\boldsymbol{\Omega}_{\boldsymbol{x}_{i+1}}} ... \int_{\boldsymbol{\Omega}_{\boldsymbol{x}_{N_D}}} \mathcal{G}((d_1, ..., d_I), (\boldsymbol{x}_1, ..., \boldsymbol{x}_I), \boldsymbol{\theta}) \\
f_{\boldsymbol{X}_{i+1}|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_i}(\boldsymbol{x}_{i+1}|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_i)...f_{\boldsymbol{X}_I|\boldsymbol{\theta},\boldsymbol{X}_1,...,\boldsymbol{X}_{I-1}}(\boldsymbol{x}_I|\boldsymbol{\theta}, \boldsymbol{x}_1, ..., \boldsymbol{x}_{I-1})\ d\boldsymbol{x}_I, ..., d\boldsymbol{x}_{i+1}.
\end{aligned} \tag{1.19}$$

This gives us Bayes' decision rule for the sequential problem. Intuitively, the optimal decision at each stage is the one that, given current information (that is, all previous data), maximises the expected value of the gain function.

2

Adaptivity in Phase II/III programmes

2.1 An introduction to adaptive designs

Statistical inference for Clinical Trials has classically been done with the assumption that the framework of the trial procedure is completely specified in advance. In particular, all confirmatory trials have the hypotheses and statistical analysis plan described in advance of the trial. In order to plan an appropriate trial design, knowledge of quantities such as the desired efficacy of a new treatment that one wishes to detect, appropriate doses or applications of the treatment, the success rate in the control group, and variability of endpoint measurements are needed. These are not typically known, but relevant information can be learnt throughout the trial. Based on information accumulated throughout the trial, it can be desirable to stipulate changes to the trial procedure.

An important factor that fuelled the research into adaptive designs was the release of the regulatory guidance ICH (1998) in both Europe and the United States stating

"If it becomes necessary to make changes to the trial, any consequent changes to the statistical procedures should be specified in an amendment to the protocol at the earliest opportunity, especially discussing the impact on any analysis and inferences that such changes may cause. The procedures selected should always ensure that the overall probability of type I error is controlled."

The publication of Bauer and Kohne (1994) and Bauer and Kieser (1999) were the first approaches to allow flexible design modifications in the middle on an ongoing trial using data that have been observed so far without inflating the type I error. Previously there was research in procedures for modifying sample size as estimates of nuisance parameters' became available (see Wittes J (1990) and Chapter 14 Jennison and Turnbull (2000)) and adaptive randomisation (see Chapter 18 Jennison and Turnbull (2000)). The focus of adaptive designs in drug research has since shifted from focusing on sample size reassessment, to including other adaptations such as treatment selection and the testing of multiple hypotheses.

The idea of adaptive designs in general is that they allow implementation of design adaptations without inflating the type I error. These adaptations can be based on the unblinded data that has been collected so far as well as any additional external information, and often the adaptations do not need to be specified in advance.

Since the release of this ICH guidance, some designs with adaptive features were accepted by regulatory bodies such as the FDA and EMA in the early 2000s. Further regulatory guidance on adaptive designs was released by the EMA (EMA (2007)) and by the FDA (of Health

(2018) and FDA (2017)). These further regulatory guidances classified approaches into those well understood and those less well understood in terms of the statistical properties and operational implementation. The role of research relating to adaptive designs is to suggest new approaches and further the understanding of current approaches.

In the rest of this section, we introduce and discuss adaptive methods that may be applied to Phase II/III programmes, which include adaptive designs with combination tests and the more traditional group sequential methods.

2.2 Adaptive designs with combination tests

2.2.1 An introduction and history

In this section, we introduce adaptive designs which use combination tests.

Let θ denote the treatment effect of the treatment of interest, and $H_0 \ : \ \theta \leq 0$ the null hypothesis that states that the treatment is not efficacious. Frequentist hypothesis testing aims to reject this null hypothesis in light of data observed in favour of the alternative, $\theta > 0$, that the treatment is efficacious.

Suppose it is of interest to test the null hypothesis against the alternative using data from 2 separate stages; stage 1 and stage 2. Pooling the data together and performing a hypothesis test in the pooled data can introduce bias if the design of the second stage is influenced by the data from the first stage. Adaptive combinations tests can be used to combine the information in stagewise calculations in a way that does not introduce bias.

Denote P_1 and P_2 the stagewise p-values for H_0 such that P_1 is based on only stage 1 data and P_2 based on only stage 2 data. We shall reject H_0 if $C(P_1, P_2) \leq c$ where C is a function increasing in P_1 and P_2 and c is a constant. We shall consider cases when P_1 and P_2 are defined such that

If $\theta = 0$, then $P_1 \sim U(0,1)$ and $P_2|P_1 \sim U(0,1)$,

If $\theta < 0$, then $P_1 > U(0,1)$ and $P_2|P_1 > U(0,1)$,

where $X > Y$ means X is stochastically greater than Y (that is, $\mathbb{P}(X > x) > \mathbb{P}(Y > x)$ for any $x \in \mathbb{R}$).

In the case that $\theta = 0$, $P_1 \sim U(0,1)$, and $P_2 \mid$ Stage 2 design $\sim U(0,1)$. If the stage 2 design is chosen based upon P_1, then $P_2 \mid P_1 \sim U(0,1)$ for all P_1. And therefore P_1 and P_2 are independent and identically distributed $U(0,1)$ random variables. Constant c is chosen such that $\mathbb{P}_0(C(P_1, P_2) \leq c) = \alpha$ for some type I error rate α. In the case when $\theta < 0$, we also then have that $\mathbb{P}_\theta(C(P_1, P_2) \leq c) < \alpha$.

The combination function may alternatively be defined by rejecting H_0 if $C(P_1, P_2) \geq c$ where C is a function decreasing in P_1 and P_2 and c is a constant.

A procedure first proposed in the 1920s by Fisher (1925) involves rejecting the null hypothesis when the product of the p-values from both stages is less than some critical value. An alternative procedure is to reject the null hypothesis when the weighted sum of the z-statistics corresponding to the p-values is greater than some critical value. We illustrate these two approaches below.

- Inverse χ^2:

$$\text{Reject } H_0 \text{ if } C(P_1, P_2) := P_1 P_2 < c_1, \tag{2.1}$$

- Inverse Normal:

$$\text{Reject } H_0 \text{ if } C(P_1, P_2) := w_1 \Phi^{-1}(1 - P_1) + w_2 \Phi^{-1}(1 - P_2) > c_2, \tag{2.2}$$

where w_1 and w_2 are arbitrary weights subject to $w_1^2 + w_2^2 = 1$.

Constants c_1 and c_2 are determined such that the test has a type I error rate α. Noting that when $P_i \sim \text{Unif}(0, 1)$ for $i = 1, 2$, we have $-2\log(P_1 P_2) \sim \chi^2_2$, we define $c_1 := \exp(-0.5\chi^2_{4,1-\alpha})$, where $\chi^2_{\eta,1-\alpha}$ is the $(1-\alpha)$ quantile of the χ^2 distribution with η degrees of freedom. Similarly, we define $c_2 := z_{1-\alpha}$ where $z_{1-\alpha}$ is the upper $1 - \alpha$ tail point of the standard normal distribution.

The two stages in this procedure may relate to recruiting patients before and after an interim analysis. The data that p_1 and p_2 are calculated from is the data collected from the patients recruited before and after the interim analysis respectively. Overall, one requires a planning stage, interim analysis, and final analysis. During the planning stage, the design of the first stage including H_0, test statistic, sample size, and the combination test are specified. At the interim analysis it is decided whether the trial is stopped early due to early rejection of H_0 or early acceptance due to futility. Otherwise the design of the second stage is specified (including the sample size, test statistic, and null hypothesis), based on information gained from the first stage, without inflating the type I error rate of the overall procedure. The final analysis is then performed after the second stage is complete.

An approach for defining a two-stage combination test in the context of an interim analysis in a clinical trial was first given by the landmark paper Bauer and Kohne (1994). In this paper, one defines the combination function $C(p_1, p_2)$, early stopping boundaries α_0, α_1, and critical value c for the final analysis. The trial is stopped after the first stage if $p_1 \leq \alpha_1$ (early rejection of H_0) or $p_1 \geq \alpha_0$ (early acceptance due to futility). The trial otherwise continues to the second stage where H_0 is rejected according to the combination test where α_1 and α_0 are chosen such that the type I error is preserved,

$$\alpha_1 + \int_{\alpha_1}^{\alpha_0} \int_0^1 \mathbb{1}_{\{H_0 \text{ rejected}\}}(p_1, p_2)\ dp_2\ dp_1 = \alpha. \tag{2.3}$$

The flexibility of the design comes from the fact the second stage (including the sample size or test statistic) can be based on data which was used to calculate p_1. The combination function may take the form of the inverse χ^2 or the inverse normal combination functions given in Equations 2.1 and 2.2.

In the case of the inverse χ^2 combination function, Equation 2.3 can be evaluated as a closed form expression:

$$\alpha_1 + c_1\ (\log(\alpha_0) - \log(\alpha_1)) = \alpha. \tag{2.4}$$

Thus to maintain the type I error rate at level α across both stages, α_0 and α_1 are computed by solving Equation 2.4. For the inverse normal combination function, one must use a root

finding algorithm to find Equation α_0 and α_1 such that Equation 2.3 is satisfied.

Various publications about adaptive designs have followed, such as Proschan and Hunsberger (1995), Cui et al. (1999), Lechmacher W (1999), and Müller and Schäfer (2001). These involve various adaptations such as modifying the sample size, identifying sub-populations for population enrichment, and dose selection whilst the type I error rate is protected.

Proschan and Hunsberger (1995) defined a 'conditional error function' which was used to adapt the sample size in an interim analysis. This involved calculating the maximum type I error rate conditional on observed data at the interim analysis that may be produced by always applying the worst case balanced sample size reassessment rule at the interim. One may perform any type of balanced sample size reassessment after adjusting for this worst case without inflating the type I error rate.

Lechmacher W (1999) and Cui et al. (1999) noted that for normal outcome variables with known variance, the final test statistic is the weighted average of stagewise z-scores weighted by the square root of the corresponding sample sizes, leading to the inverse normal combination function defined above. When no adaptation has been performed then the conventional sufficient z-test can be performed in the usual way.

2.2.2 Multiple testing

In a clinical trial, it may be the case that there will be interest in testing more than one single hypothesis. Multiple hypotheses may result from testing primary and secondary endpoints, having multiple treatments, or considering subgroups within the population. Thus multiple testing becomes an important topic in many of the research areas in adaptive methods described in the previous section. Methods have been developed to study different hypotheses at once. In order to satisfy regulators, protecting the type I error rate is essential in most drug development programs. Therefore it is of utmost importance that the probability of rejecting at least one true hypothesis should be bounded by a fixed pre-determined α, irrespective of how many and which null hypotheses are in fact true.

Let us consider the case of K parameters θ_i $(i = 1, ..., K)$. Each may represent the true mean endpoint difference between treatment i and the control, or the true mean endpoint difference between a treatment and control in patient subgroup i, or the true mean endpoint difference between treatment versus control for endpoint i.

Write the K null hypotheses as

$$\begin{aligned} H_1 &: \theta_1 \leq 0, \\ H_2 &: \theta_2 \leq 0, \\ &\vdots \\ H_K &: \theta_K \leq 0. \end{aligned} \tag{2.5}$$

Each hypothesis can be true or false depending on the values of θ_1,...,θ_K. During a test procedure, any number of these hypotheses may be rejected.

An intersection hypothesis $H_{\mathcal{I}}$ is defined for subset $\mathcal{I} \subseteq \{1, ..., K\}$ as

$$H_{\mathcal{I}} := \bigcap_{i \in \mathcal{I}} H_i. \tag{2.6}$$

Suppose we are interested in testing intersection hypothesis $H_{\mathcal{I}}$ at level α. Let $p_1, ..., p_K$ denote the observed p-values and $z_1, ..., z_K$ denote the observed Z-statistics for each of the parameters θ_i and let the p-values of parameters in $\mathcal{I}$ be $p_{(1)}, ...p_{(N)}$ in increasing order. Several approaches have been developed to test $H_{\mathcal{I}}$ at level α, and we outline three below.

- Bonferroni (Bonferroni (1936))
  Reject $H_{\mathcal{I}}$ if $p_{(1)} \leq \alpha/N$
- Simes (Simes (1986))
  Reject $H_{\mathcal{I}}$ if $p_{(i)} \leq i\alpha/N$ for at least one $i = 1, ..., N$.
- Dunnett (Curnow and Dunnett (1962))
  Reject $H_{\mathcal{I}}$ if $p_{\mathcal{I}} \leq \alpha$
  where $p_{\mathcal{I}} := \mathbb{P}_{\mathbf{0}}(\max(Z_{\mathcal{I}}) \geq \max_{i \in \mathcal{I}} z_i)$ and $Z_{\mathcal{I}}$ is the multivariate normal distribution of Z-statistics of the parameters in $\mathcal{I}$. The form this takes depends upon what the parameters θ_i represent. In Section 2.2.3, we use this test in the context of θ_i representing the true mean endpoint difference between treatment i and control.

Define the FWER as

$$\text{FWER} := \sup_{\boldsymbol{\theta}} \mathbb{P}_{\boldsymbol{\theta}}(\text{Reject} \geq 1 \textit{ true} \text{ hypotheses}) \tag{2.7}$$

We say a procedure preserves the FWER strongly at α if

$$FWER \leq \alpha. \tag{2.8}$$

The closed testing procedure Marcus et al. (1976) states that a null hypothesis H_i can be rejected only if

- H_i is rejected itself with a level α test, and
- All intersection hypotheses $H_{\mathcal{I}}$ such that $i \in \mathcal{I}$ are rejected each with level α tests.

The closed testing procedure preserves the FWER strongly at α. The proof of this is simple and is outlined below.

Proof. Define $\mu_0 :=$ set of true null hypotheses, $H_{\mu_0} := \cap_{i \in \mu_0} H_i$, and the events $A :=$ reject at least one true hypothesis in the overall testing procedure, and $B :=$ reject H_{μ_0}.

Then because $A \subseteq B$ and $p(B) \leq \alpha$, we have

$$\begin{aligned} p(A) &= p(A \cap B) \\ &= p(B)\ p(A|B) \leq \alpha. \end{aligned} \tag{2.9}$$

□

The closed testing procedure is a way to construct multiple testing strategies in adaptive designs using combination tests.

2.2.3 Multiple testing within a two stage procedure with treatment selection

In the studies in this chapter, we are primarily concerned with Phase II/III programmes, which use combination tests in 2 stage procedures. Therefore we concentrate here on defining a hypothesis test over two stages that protects the FWER in the strong sense.

In particular, suppose there are K treatments with treatment effects θ_i and null hypotheses $H_i : \theta_i \leq 0$ for $i = 1, ..., K$. In the first stage, all treatments are tested against control and p-values obtained for each treatment $p_{1,1}, ..., p_{K,1}$. Using the method of Dunnett, one may compute p-values $p_{\mathcal{I},1}$ for intersection hypothesis $H_{\mathcal{I}}$ for any subset $\mathcal{I} \subseteq \{1, ..., K\}$.

Due to the adaptive nature of the test, treatments may have been dropped from the set of hypothesis to be tested. As there may be no second stage data for some null hypotheses which were dropped at the interim analysis, one may question how to obtain the second stage p-value for some intersection hypotheses which need to be rejected in order to reject the elementary hypothesis of a treatment. A valid p-value to use for the intersection hypothesis containing a dropped treatment is the p-value of of the intersection hypothesis containing all the treatments in the original intersection hypothesis that have not been dropped. Bretz et al. (2006) and Schmidli et al. (2005) discuss this in more detail.

Suppose in particular that one treatment is chosen to continue to the second stage and denote the index by i^*. This choice of treatment may be chosen based on the results of the first stage, meaning the procedure is adaptive. This may typically be the best performing treatment from the first stage, such that the treatment with the lowest p-value, but we do not assume that this is the case.

We apply the closed testing procedure with an inverse normal combination test over the two stages:

Rejects H_{i^*} if

$$C(p_{\mathcal{I},1}, p_{\mathcal{I},2}) \geq z_{1-\alpha}, \text{ for all } \mathcal{I} \text{ such that } i^* \in \mathcal{I}. \tag{2.10}$$

Since no Phase III data is available for any treatment other than i^* in Phase III, one may write Equation 2.10 as

$$\max_{\mathcal{I}: i^* \in \mathcal{I}} C(p_{\mathcal{I},1}, p_{i^*,2}) \geq z_{1-\alpha}. \tag{2.11}$$

Assuming the combination function is increasing in its left argument, we may write this as

$$C\left(\max_{\mathcal{I}: i^* \in \mathcal{I}} p_{\mathcal{I},1}, p_{i^*,2}\right) \geq z_{1-\alpha}. \tag{2.12}$$

That is,

$$C(\tilde{p}_{i^*,1}, p_{i^*,2}) > z_{1-\alpha}, \tag{2.13}$$

where multiplicity adjusted p-value $\tilde{p}_{i^*,1}$ is defined as $\tilde{p}_{i^*,1} := \max_{\mathcal{I}: i^* \in \mathcal{I}} p_{\mathcal{I},1}$.

Equation 2.13 provides a test to reject H_{i^*} that intuitively combines the multiplicity adjusted p-value from the first stage with the p-value from the second stage which strongly protects the FWER. In Chapter 3, we use this equation as the hypothesis test for a Phase II/III programme.

Hampson and Jennison (2015) compare several different combination functions and multiple testing procedures. The rule considered here, with the inverse normal combination test with

a Dunnett multiplicity adjustment, is considered one of the rules which performs well over a variety of situations and is recommended in practice.

2.3 Group sequential designs

2.3.1 The development of group sequential design methodology

Monitoring the results of a trial as they occur with a view to either modify the trial or have an early termination seems natural in many settings. Having interim analyses in a trial can be considered advantageous for various reasons. These reasons can be ethical, administrative, and economic.

For trials with human subjects, ethically one would want to not have subjects exposed to unsafe or ineffective treatments. Therefore it is desirable to terminate the trial as soon as possible in this case. Administratively, interim analyses provide a point at which one can check the interim results show the experiment is being executed as planned, and any assumptions made when designing the trial still apply, and action can be taken if not. For a trial that has a positive result, stopping early for efficacy means the treatment can then be released sooner, meaning a greater amount of time in the treatment's patent life can be exploited. Alternatively, if the trial does not have a positive result, stopping early saves resources that can then be diverted towards other treatments.

In this section we describe the background relating to group sequential methods as they are understood today, and outline the theory behind some of the popular group sequential methods used in this thesis.

Armitage (1993) note that the theory of experimental design has classically dealt with experiments with a predetermined size, perhaps due to the pioneering work of Fisher (1925) in agricultural research, where the outcome of a field trial is available only after a long time after the experiment was designed. Wald (1947) and Barnard (1946) developed sequential analysis theory when participating in industrial groups for production during the war effort in World War II. An example of this was the sequential probability ratio test. Wald and Wolfowitz (1948) showed the procedure had the smallest possible expected sample size amongst all tests with type I and II error probabilities bounded by certain values. However, the sample size was not bounded.

The triangular group sequential tests were developed by Lorden (1976). For tests which select from more than two hypotheses, the book of Bechhofer et al. (1968) provides an overview. Hewett and Spurrier (1983) provides a review of early approaches that containing two or three stages with normal responses. In these approaches, repeated numerical integration was required to find the properties of the designs. This method is now a key tool to construct group sequential tests, such as in Jennison and Turnbull (2000).

Pocock (1977) gave a clear method for implementing a group sequential design which had fixed type I and II error rates, whilst noting the generalisability of the approach, where a group sequential design for normal responses could be used for other responses. O'Brien and Fleming (1979) proposed a different class of group sequential designs with different stopping boundaries. In comparison to the Pocock approach, these stopping rules were more conservative and had stopping rules more similar to the fixed sample design if the final stage was reached. Lan and DeMets (1983) proposed new methods to be applied even when the

group sizes are unequal or unpredictable. This permitted methods to be extended to survival data where the group sizes, or increments in information, are unequal and unpredictable.

DeMets and Ware (1980), DeMets and Ware (1982), and Whitehead (1986) modified the boundaries of group sequential designs by allowing early stopping to accept the null hypothesis.

Upon termination of a trial, inferences may be necessary. This may be of confidence intervals (Siegmund (1978), Pollak and Siegmund (1985), Kim and DeMets (1987)), p-values (Fairbanks and Madsen (1982), Fairbanks et al. (1982)), or point estimates (Whitehead (1986)). Different outcomes to a group sequential test have different numbers of observations. Therefore the monotone likelihood ratio property does not apply so one may define the ordering of the sample space which construct the p-values.

2.3.2 The canonical distribution

In Jennison and Turnbull (2000), the canonical distribution of the test statistics is formulated, which is the basis for the interactive integration techniques that underpin the computations of most group sequential designs. We describe an overview of this theory here.

Suppose that we have a group sequential design with K analyses with cumulative Z-statistics of $\{Z_1, ..., Z_K\}$. One says that $\{Z_1, ..., Z_K\}$ follow the canonical distribution with information levels $\{\mathcal{I}_1, ..., \mathcal{I}_K\}$ if

$$\begin{aligned} &(Z_1, ..., Z_K) \text{ is multivariate normal,} \\ &\mathbb{E}(Z_k) = \theta\sqrt{\mathcal{I}_k}, \text{ for } k = 1, ..., K, \\ &Cov(Z_{k_1}, Z_{k_2}) = \sqrt{\mathcal{I}_{k_1}/\mathcal{I}_{k_2}} \text{ for } k_1 < k_2. \end{aligned} \tag{2.14}$$

It follows that any $\{Z_1, ..., Z_K\}$ that has this distribution conditional on $\{\mathcal{I}_1, ..., \mathcal{I}_K\}$ is a Markov sequence. This property is useful when simplifying calculations when constructing groups sequential designs using iterative integration techniques as in Chapter 19 of Jennison and Turnbull (2000). The set $\{\mathcal{I}_1, ..., \mathcal{I}_K\}$ corresponds to the Fisher information levels for the statistical test.

Consider the case when the treatment and control responses are distributed as $X_i^{(t)} \sim N(\mu_1, \sigma^2)$ and $X_i^{(c)} \sim N(\mu_0, \sigma^2)$ respectively, where the variance σ^2 is known. Let the treatment effect be denoted by $\theta = \mu_1 - \mu_0$ with null hypothesis $H_0 : \theta \leq 0$. Suppose n_k is the cumulative sample size per group in a group sequential trial with K analyses. The maximum likelihood estimator of θ at analysis k is

$$\hat{\theta}_k = \sum_{i=1}^{n_k} (X_i^{(t)} - X_i^{(c)})/n_k. \tag{2.15}$$

The Fisher information may be written as

$$\mathcal{I}_k = n_k/(2\sigma^2), \tag{2.16}$$

and one has $\hat{\theta}_k \sim N(\theta, \mathcal{I}_k^{-1})$ for $k = 1, ..., K$.

Letting $Z_k = \hat{\theta}_k\sqrt{\mathcal{I}_k}$, we have that $\{Z_1, ..., Z_K\}$ follow the canonical distribution defined above. Jennison and Turnbull (2000) describes many other situations in which the Fisher information and Z-statistics can be defined such that they follow the canonical distribution.

These include parallel two-treatment comparisons, testing the mean of a single population, paired two-treatment comparisons, two-period crossover trials, binary data, survival data, tests with unknown variance, and linear and other parametric models. Thus group sequential trials can be used in a large number of different settings.

2.3.3 Some examples of one sided group sequential trials

Using the notation of Jennison and Turnbull (2000), we outline a few of the group sequential designs that are used in this thesis below. Whilst much of the literature on group sequential designs is of two sided testing, in clinical trials we often are interested in one sided hypothesis tests. That is, if θ is the true treatment effect of the treatment relative to placebo, rejecting $H_0 : \theta \leq 0$ will provide evidence that the drug is successful.

For any one sided group sequential design, one observes test statistics $(Z_1, ..., Z_K)$ at information levels $(\mathcal{I}_1, ..., \mathcal{I}_K)$. The group sequential trial consists of rejection boundaries $\{b_1, ..., b_K\}$ and acceptance boundaries $\{a_1, ..., a_K\}$. At analysis k, one rejects H_0 if $Z_k \geq b_k$ or accepts H_0 if $Z_k < a_k$. Otherwise, one continues to the next stage.

Pampallona Tsiatis power family one-sided designs

The first designs we consider are the Pampallona and Tsiatis (1994) power family of one sided tests.

For a power family test with parameter Δ, the rejection and acceptance boundaries are

$$\begin{aligned} b_k =& c^{(1)}_{K,\alpha,\beta,\Delta}(k/K)^{\Delta-1/2} \\ a_k =& \delta\sqrt{\mathcal{I}_k} - c^{(2)}_{K,\alpha,\beta,\Delta}(k/K)^{\Delta-1/2} \end{aligned} \tag{2.17}$$

for $k = 1, ..., K$.

The critical values are found that satisfy the type I and II error rates and enforce $a_K = b_K$. Although designed for a specific sequence of information levels, these designs can still be used when the information levels differ from the planned ones with small perturbations in type I and II error probabilities.

ρ-family Error Spending Designs

Most group sequential designs are designed for a fixed number of equally sized groups of information levels. Error spending designs provide a flexible design which may cope with unpredictable information sequences whilst preserving the type I error exactly. In addition, the number of analyses does not need to be fixed in advance.

Lan and DeMets (1983) proposed spending type I and II error throughout the trial as a function of the observed information, with a specified target for the maximum information $\mathcal{I}_{max}$. This was done in the context of a two-sided test which we adapt here for a one-sided test. One must define error spending functions f and g which allocate the type I and II error to be spent $\pi_{1,i}$ and $\pi_{2,i}$ at each analysis i according to

$$\begin{aligned} \pi_{1,1} &= f(\mathcal{I}_1/\mathcal{I}_{max}) \\ \pi_{1,k} &= f(\mathcal{I}_k/\mathcal{I}_{max}) - f(\mathcal{I}_{k-1}/\mathcal{I}_{max}) \text{ for } k = 2, 3, ..., K \\ \pi_{2,1} &= g(\mathcal{I}_1/\mathcal{I}_{max}) \\ \pi_{2,k} &= g(\mathcal{I}_k/\mathcal{I}_{max}) - g(\mathcal{I}_{k-1}/\mathcal{I}_{max}) \text{ for } k = 2, 3, ..., K. \end{aligned} \tag{2.18}$$

The rho family error spending designs when one uses the following error spending functions

$$\begin{aligned} f(t) &= \min(\alpha t^{\rho_1}, \alpha) \\ g(t) &= \min(\beta t^{\rho_2}, \beta) \end{aligned} \tag{2.19}$$

for some parameters $\rho_1 > 0$ and $\rho_2 > 0$.

At each stage k, the acceptance and rejection boundaries are calculated for that stage. One does this by solving for a_k and b_k in the following equations,

$$\begin{aligned} \mathbb{P}_0(a_1 < |Z_1| < b_1, ..., a_{k-1} < |Z_{k-1}| < b_{k-1}, |Z_k| \geq b_k\} &= \pi_{1,k} \\ \mathbb{P}_\delta(a_1 < |Z_1| < b_1, ..., a_{k-1} < |Z_{k-1}| < b_{k-1}, |Z_k| < a_k\} &= \pi_{2,k}. \end{aligned} \tag{2.20}$$

Once one reaches a maximum information $\mathcal{I}_{max}$, one stops and performs a interim analysis at this point, where the rejection boundary a_K is chosen to be equal to b_K, where b_K is chosen such that the required type I error is spent according to the first equation in Equations 2.20.

Chapter 19 in Jennison and Turnbull (2000) provides methods to numerically compute designs for both designs considered here. These are iterative integrative and root solving calculations, which rely on the properties of the canonical distribution.

3

The Value of Adaptivity in a Phase II/III Programme with Treatment Selection

3.1 Introduction

As remarked in Chapter 1, studying Phase II and III together as a Phase II/III programme can be advantageous relative to studying each phase separately. A Phase II/III programme with treatment selection is a II/III programme which has multiple treatments entering Phase II, with some treatments dropped before Phase III commences. The aim of the programme is two-fold: to select an efficacious treatment, and to obtain sufficient evidence of its efficacy for regulatory approval.

In this chapter we consider Phase II/III programmes with treatment selection in the case when only one treatment is chosen for Phase III, when one observes the primary endpoint in both phases, and when no dose response relationship is assumed between the treatments.

In Chapter 2, we considered adaptive methods which can be applied to a Phase II/III programme. We shall examine the value of some of these adaptive methods in this setting.

During a Phase II/III programme with treatment selection, one must make decisions about the next part of the programme. In particular:

Pre-Phase II decisions:

- Phase II sample size

Pre-Phase III decisions:

- Phase III sample size

- Treatment to take forward

In order to fairly compare programmes against one another, we require each programme to be fully optimised. This involves having an optimal decision rule for the Pre-Phase III decisions based on the Phase II data, and an optimal Phase II sample size.

We compute these optimal decision rules using Bayesian decision theory introduced in Section 1.3. We initially use a simple form of gain function to quantify the value of the programme, but we go on to consider more detailed forms of the gain function later in Section 3.5.1.

3.2 Motivations from previous research

In Section 1.1.1, we considered previous literature that addressed optimising Phase II/III as a programme. Below, we consider the Parke et al. (2017) approach in greater detail, as this provides motivation for the approach taken in this chapter.

3.2.1 Parke et al. (2017)

In this paper, eight programmes are compared against each other. These eight programmes were constructed from different Phase II and III designs. The following Phase II designs are considered:

- 2 concurrent two arm Phase II trials, with a different new treatment compared against a common control in each,
- a three arm Phase II trial, with 2 different new treatments compared against control,
- a three arm Phase II trial with an interim analysis where either or both new treatments can be dropped,
- a three arm Phase II trial with multiple interim analyses where either or both new treatments can be dropped, and
- a three arm Phase II trial with response adaptive randomisation and multiple interim analyses where either or both new treatments can be dropped.

In all, eight programmes were defined by combining the above Phase II designs with fixed sample or group sequential Phase III designs. Not all combinations of Phase II design were used with each Phase III design. The group sequential Phase III designs were error-spending group sequential designs as introduced in Section 2.3.

The programmes are compared using their expected Net Present Value (eNPV), representing the value, in terms of financial viability, of a programme. The model is similar to the Financial Model introduced in Section 1.5.1.

The paper concluded by finding that there was a distinct improvement for programmes with increasing amounts of adaptivity. That is, introducing each new statistical technique brought added value to the programme. The best performing programme was the one with a three-arm Phase II with many interim and response adaptive randomisation, with a four interim analysis group sequential Phase III design.

There are several limitations with the approach taken in this paper which we aim to overcome in our approach.

Many of the programmes contained rigid rules which were not optimised. In particular, all the programmes stipulate that the treatment effects must have a predictive probability of success greater or equal to a pre-determined threshold before being considered for a Phase III trial. While these may be desirable as they match benchmark tests which have been used in industry, more general decision rules lead to higher values of eNPV.

In all the programmes, Phase III is treated as separate with a hypothesis test using data from this phase only. We shall extend this approach to consider the use of combination tests as introduced in Section 2.2.

One major concern of the programmes studied is that none allow adapting the Phase III sample size based on the observed Phase II data. Using a sample size for Phase III that is fixed before Phase II begins is an unrealistic assumption for such a setting as Phase III trials are expensive and trial management teams will make decisions about Phase III after seeing the results of Phase II. Therefore it is desirable to study programmes with sample size re-estimation rules between Phase II and III in all programmes. If these rules are optimised for each programme, one may compare the programmes fairly.

Notation

Below, we list notation associated with this approach. Contextual definitions are given in relevant places later in the text.

Global Parameters

K	Number of new treatments entering the Phase II/III programme.
$\boldsymbol{\theta}$	Vector of length K of the true treatment effects.
σ^2	The variance of all responses on control and new treatment arms.
$\boldsymbol{\theta}_0, \Sigma_0$	Hyperparameters of the prior distribution for the vector of treatment effects $\boldsymbol{\theta}$.
G	The gain associated with rejecting the null hypothesis for an efficacious treatment.
γ_1	Cost associated with treating a Phase II patient.
γ_2	Cost associated with treating a Phase III patient.
$\mathfrak{I}_0$	$(\sigma^2, G, \gamma_1, \gamma_2, \boldsymbol{\theta}_0, \Sigma_0)$. The set of global parameters known at the beginning of the programme.

Parameters and observed data associated with Phase II

$n_1^{(t)}$	The sample size per treatment arm in Phase II.
$n_1^{(c)}$	The sample size for the control arm in Phase II.
$\hat{\boldsymbol{\theta}}_1$	$(\hat{\theta}_{1,1}, \hat{\theta}_{2,1}, ..., \hat{\theta}_{K,1})$, The maximum likelihood estimators of the treatment effects $\boldsymbol{\theta}$ based on Phase II data.
$\boldsymbol{p}_1$	$(p_{1,1}, p_{2,1}, ..., p_{K,1})$. P-values for testing $H_1, ..., H_K$ corresponding to $\hat{\boldsymbol{\theta}}_{\mathbf{1}}$, where the hypotheses $H_1, ..., H_K$ are to be defined in the following text.
$\tilde{\boldsymbol{p}}_1$	$(\tilde{p}_{1,1}, \tilde{p}_{2,1}, ..., \tilde{p}_{K,1})$. Multiplicity adjusted p-values corresponding to $\boldsymbol{p}_1$.
$\mathfrak{I}_1$	$(\mathfrak{I}_0, \hat{\boldsymbol{\theta}}_1, n_1^{(t)}, n_1^{(c)})$. The set of cumulative summary statistics formed from $\mathfrak{I}_0$ plus summary statistics from Phase II.

Parameters and observed data associated with Phase III

i^*	The index of the treatment chosen to continue to Phase III.
n_2	The sample size per treatment and control arm in Phase III. If Phase III is group sequential, this is the maximum sample size per treatment.
S	If Phase III is group sequential, this is the number of stages of the group sequential design.

$n_2^{(obs)}$ If Phase III is group sequential, this is the observed sample size per treatment arm. If not, this is equal to n_2.

$\hat{\theta}_{i^*,2}$ The maximum likelihood estimate of the treatment effect of treatment i^* based on the Phase III data only.

$p_{i^*,2}$ The p-value corresponding to $\hat{\theta}_{i^*,2}$ for testing hypothesis $H_{i^*} : \theta_{i^*} \leq 0$, which is to be defined in the folowing text.

$\mathfrak{I}_2$ $(\mathfrak{I}_1, \hat{\theta}_{i^*,2}, n_2)$ The set of cumulative summary statistics formed from $\mathfrak{I}_1$ plus summary statistics from Phase III.

Other Parameters and Functions

$\mathcal{G}$ The gain function of an observed programme.

α The familywise error rate of the overall programme and testing procedure.

$C(\cdot, \cdot)$ The inverse normal combination function (see Section 2.2) used to combine Phase II and III p-values into a test statistic.

3.3 Our Phase II/III programme framework

Suppose K treatments are to be considered at the start of the programme with no dose response relationship assumed. Suppose the primary responses are normally distributed with known variance σ^2, and means $\mu_i^{(t)}$ for treatments $i = 1, ..., K$ and $\mu^{(c)}$ for control. Define vector $\boldsymbol{\theta} := (\theta_1, ..., \theta_K)$ as the treatment effect vector where $\theta_i = \mu_i^{(t)} - \mu^{(c)}$ for $i = 1, ..., K$. A high treatment effect will indicate a successful treatment compared to control. We assume that primary responses are observed in both Phase II and III.

The vector $\boldsymbol{\theta}$ is considered unknown and inference is performed on it during the programme. Define K one-sided null hypotheses $H_1 : \theta_1 \leq 0$, ... ,$H_K : \theta_K \leq 0$.

The programme has an interim analysis after Phase II which is flexible, allowing the choice of which treatment to take forward i^* and the sample size n_2 for Phase III. The hypothesis that is tested at the end of the programme is H_{i^*}. Phase II data may still be incorporated in the final hypothesis test through the use of a combination function and Phase III may use group sequential methods. Below, we specify how the programme progresses with a schematic shown in Figure 3-1.

■ **Pre-Phase II Decision Making (Decision 1)**

Choose the Phase II sample size for each treatment arm ($n_1^{(t)}$) and control arm ($n_1^{(c)}$).

■ **Phase II**

Randomise $n_1^{(t)}$ patients to each treatment $i = 1, ..., K$ and $n_1^{(c)}$ to the control arm. Upon observing patient responses, the maximum likelihood estimates $\hat{\boldsymbol{\theta}}_1$ are calculated, and the p-values $\boldsymbol{p}_1$ deduced.

■ **Interim Decision Making (Decision 2)**

Based upon the Phase II data, choose the Phase III sample size per treatment arm (n_2) and treatment for Phase III (i^*).

■ **Phase III**

Randomise n_2 patients to both the treatment and control arm. In the case that Phase III is group sequential with S analyses, n_2 is the maximum number of patients on each treatment arm. Denote by $n_2^{(obs)}$ the observed number of patients on each of the treatment and control arms. If Phase III is not group sequential, $n_2^{(obs)}$ is n_2. The maximum likelihood estimate of the true treatment effect of treatment i^* based on the Phase III data only, $\hat{\theta}_{i^*,2}$, and corresponding p-value $p_{i^*,2}$ are calculated.

■ **Final Analysis**

One performs a hypothesis test with null hypothesis H_{i^*}. This hypothesis test makes use of Phase III data but may or may not additionally use Phase II data.

If the test makes use of Phase III data only, one performs a standard Z-test comparing treatment against control.

If both Phase II and Phase III data is used in the hypothesis test, the p-values from Phase II and III are combined in the combination function used to perform the hypothesis test. Formally, one rejects H_{i^*} if and only if

$$C(\tilde{p}_{i^*,1}, p_{i^*,2}) > z_{1-\alpha}, \tag{3.1}$$

where the inverse-normal combination function $C(\cdot,\cdot)$ and multiplicity adjusted p-value $\tilde{p}_{i^*,1}$ defined in Section 2.2.3. This test protects the familywise error rate of the two stage procedure strongly at level α.

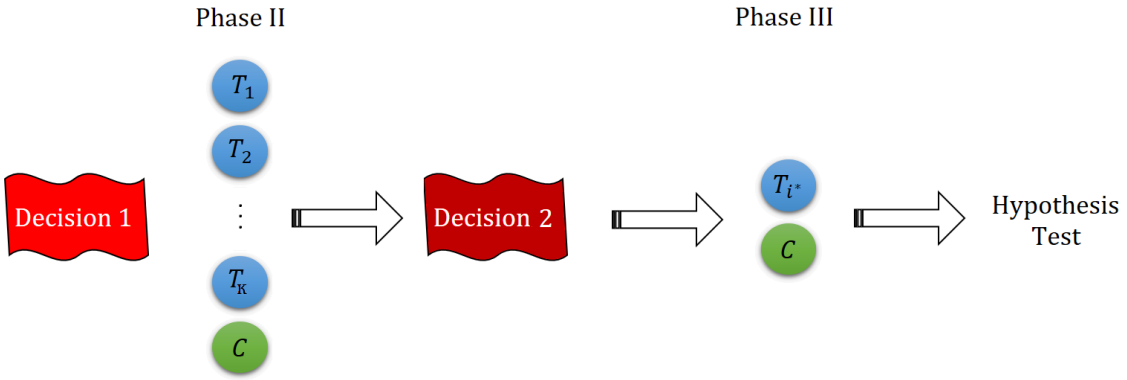

Figure 3-1: A schematic showing the locations of Decisions 1 and 2.

3.3.1 Gain function

As discussed in Section 1.3, in order to make decisions throughout the programme using Bayesian decision theory, the value of particular outcomes of the programme need to be specified numerically with a gain or utility function. We use a simple gain function.

One defines constant a G and function ζ such that $G\zeta(\theta_{i^*})$ is the value to the sponsor of rejecting H_{i^*}, given the true treatment effect was θ_{i^*}. Positive real numbers γ_1, γ_2 are defined as the cost of treating a patient in Phase II and III respectively. The gain function is hence defined as

$$\mathcal{G}(\mathfrak{I}_2, \theta_{i^*}) := G\ \zeta(\theta_{i^*})\ \mathbb{1}_{\{H_{i^*} \text{ is rejected}\}} - \gamma_1(Kn_1^{(t)} + n_1^{(c)}) - 2\gamma_2 n_2. \tag{3.2}$$

Table 3.1: Four Phase II/III Programmes with different components.

	Dec. 1	Phase II	Dec. 2	Phase III	Hypothesis Test
1	Choose: $n_1^{(t)}$, $n_1^{(c)}$	Fixed Sample; $n_1^{(t)}$ per treatment $n_1^{(c)}$ for control	Choose: i^*, n_2	Fixed Sample; n_2 patients per arm	Phase III data only
2	Choose: $n_1^{(t)}$, $n_1^{(c)}$	Fixed Sample; $n_1^{(t)}$ per treatment $n_1^{(c)}$ for control	Choose: i^*, n_2	Fixed Sample; n_2 patients per arm	Combination Test with Phase II, III data
3	Choose: $n_1^{(t)}$, $n_1^{(c)}$	Fixed Sample; $n_1^{(t)}$ per treatment $n_1^{(c)}$ for control	Choose: i^*, n_2	GSD; max. n_2 patients per arm	Phase III data only
4	Choose: $n_1^{(t)}$, $n_1^{(c)}$	Fixed Sample; $n_1^{(t)}$ per treatment $n_1^{(c)}$ for control	Choose: i^*, n_2	GSD; max. n_2 patients per arm	Combination Test with Phase II, III data

3.3.2 Components of the programmes

To assess the value of adding components to bring adaptivity to a programme, one may define the 4 programmes given in Table 3.1. The first two have a fixed sample Phase III design whilst the latter two apply a group sequential design (GSD). Programmes 1 and 3 use Phase III data only in the hypothesis test H_{i^*} whilst Programmes 2 and 4 use data from both Phase II and III in a combination test as described in Section 2.2.3 for hypothesis test H_{i^*}.

Choosing $n_1^{(t)}$ and $n_1^{(c)}$

We suppose the number of patients $n_1^{(t)}$ on each treatment arm and $n_1^{(c)}$ on control arm satisfy the relation $n_1^{(c)} = \sqrt{K} n_1^{(t)}$. This relation minimises the variance of each maximum likelihood estimator $\text{Var}(\hat{\theta}_i)$ for each i, subject to a given total sample size and equal numbers of observations for each new treatment. Given this, the choice in Decision 1 reduces down to a choice of $n_1^{(t)}$ only, from which $n_1^{(c)}$ can be deduced.

Combining the GSD with a Combination Test in Programme 4

The group sequential design for Phase III is used with the inverse normal combination test in the following way. Suppose $\tilde{p}_{i^*,1}$ is the multiplicity adjusted p-value observed from Phase II. Let p^* be the solution of

$$C(\tilde{p}_{i^*,1}, p^*) = z_{1-\alpha}. \tag{3.3}$$

The group sequential design for Phase III is then constructed with type I error rate of p^*. Then one crosses the rejection boundary of this group sequential test if and only if H_{i^*} is rejected in the combination test.

Comparing the Programmes

Given that the optimal decision rules are calculated so that one may make optimal decisions at each decision point, the expected value of the gain function of the optimal decision at Decision 1 represents the total value of the programme. We denote this quantity $\mathcal{D}_{\mathcal{J}_0}^{(1)}$ and derive its form in Section 3.6.3.

By comparing the value of each of the programmes, one can examine the value of all the components of a programme. In the following section, we describe an example of a simulation study that does this for the four programmes described above.

3.4 An example: A simulation study to assess the benefit of adaptivity to the programme

3.4.1 Programme inputs and parameters

Unless stated otherwise, in our simulation study we use the following values for the parameters:

Programme Parameters:	*Gain Function Parameters:*	*GSD Parameters:*
$\alpha = 0.025$	$G = 20000$	$S = 5$
$K = 4$	$\gamma_1 = 1$	$\Delta = 0.25$
$\sigma = 3$	$\gamma_2 = 1$	
	$\zeta(\theta_{i*}) = 1$ for all θ_{i*}	

- The prior for the treatment effects was $\boldsymbol{\theta} \sim N(\boldsymbol{\theta}_0, \Sigma_0)$ with $\boldsymbol{\theta}_0 = \mathbf{0}$ and covariance matrix

$$[\Sigma_0]_{i,j} = \begin{cases} 3 & \text{if } i = j \\ 1 & \text{if } i \neq j \end{cases}. \tag{3.4}$$

  The form of this prior means that the computations are simplified. This is discussed in Section 3.6.1.

- The inverse normal combination test was used with weightings of $w_1 = \sqrt{0.15}$ and $w_2 = \sqrt{0.85}$ for Programme 2 and $w_1 = \sqrt{0.075}$ and $w_2 = \sqrt{0.925}$ for Programme 4. We discuss this choice of weightings later in this section.

- GSDs were of the Δ-family Pampallona and Tsiatis (1994) type.

- The values $n_1^{(t)}$ could take were $(30, 35, 40, ..., 115, 120)$ and values of n_2 were $(0, 100, 200, ..., 2000)$.

- The number of Monte Carlo simulations to compute an estimate of the expected gain for each $n_1^{(t)}$ in Decision 1 (see Section 3.6.3) were chosen such that the standard error of the estimate was less than 20 for Programmes 1 and 2, and less than 50 for Programmes 3 and 4, and the standard error of the difference between any two programmes at the same value of $n_1^{(t)}$ was less than 20. These small errors may be obtained by coupling estimates, as explained in Section 1.6.

3.4.2 Simulation study results

In the table below, we summarise the optimised programmes for Programmes 1 to 4, and list their properties.

Table 3.2: Properties for each optimised programme.

Programme	**1**	**2**	**3**	**4**
Optimal $n_1^{(t)}$	70	85	60	65
Expected Gain	14 299	14 401	14 800	14 830
Standard Error	20	20	48	41
PLA	77.5%	77.8%	78.6%	78.5%
Mean Optimal n_2	369	289	649	555
Expected PLSS	1157	1088	885	835
PLP at $\boldsymbol{\theta} = (0, 0, 0, 0)$	2.5%	2.5%	2.5%	2.5%
PLP at $\boldsymbol{\theta} = (1, 1, 1, 1)$	98.4%	99.7%	99.6%	100.0%
PLP at $\boldsymbol{\theta} = (0, .3, .7, 1)$	96.3%	98.7%	98.7%	99.5%
PLP at $\boldsymbol{\theta} = (0, .2, .2, .4)$	68.6%	69.3%	74.1%	74.1 %
PLP at $\boldsymbol{\theta} = (0, 0, 0, 1)$	94.4%	96.9%	96.9%	97.5%

PLA refers to programme level assurance (the probability of rejecting the null hypothesis of any treatment in the programme given the treatment effects $\boldsymbol{\theta}$ are distributed according to their prior distribution).

Mean Optimal n_2 denotes the mean of the choice of n_2 (for group sequential designs this is the maximum sample size per arm) given it is chosen optimally according to Decision 2, and the treatment effects are distributed according to the prior distribution.

Expected PLSS refers to the expected programme level sample size (the expected total sample size across all treatments and phases given the treatments effects are distributed according to the prior distribution).

PLP denotes programme level power (the probability that a null hypothesis from any treatment is rejected in a programme, given the set of treatment effects of the treatments that enter it are given by some vector $\boldsymbol{\theta}$).

Decision 1

The three plots in Figure 3-2 give the expected gain, programme level power, and programme level sample size of each programme for different values of $n_1^{(t)}$ considered in Decision 1.

Decision 2

The four plots in Figure 3-3 show the optimal n_2 as a function of the posterior mean of the treatment effect θ_{i^*}. Figure 3-4 shows the expected gain of the programme in Decision 2 as the posterior mean varies given the Phase II sample size has an optimal value of $n_1^{(t)}$ as in Table 3.2.

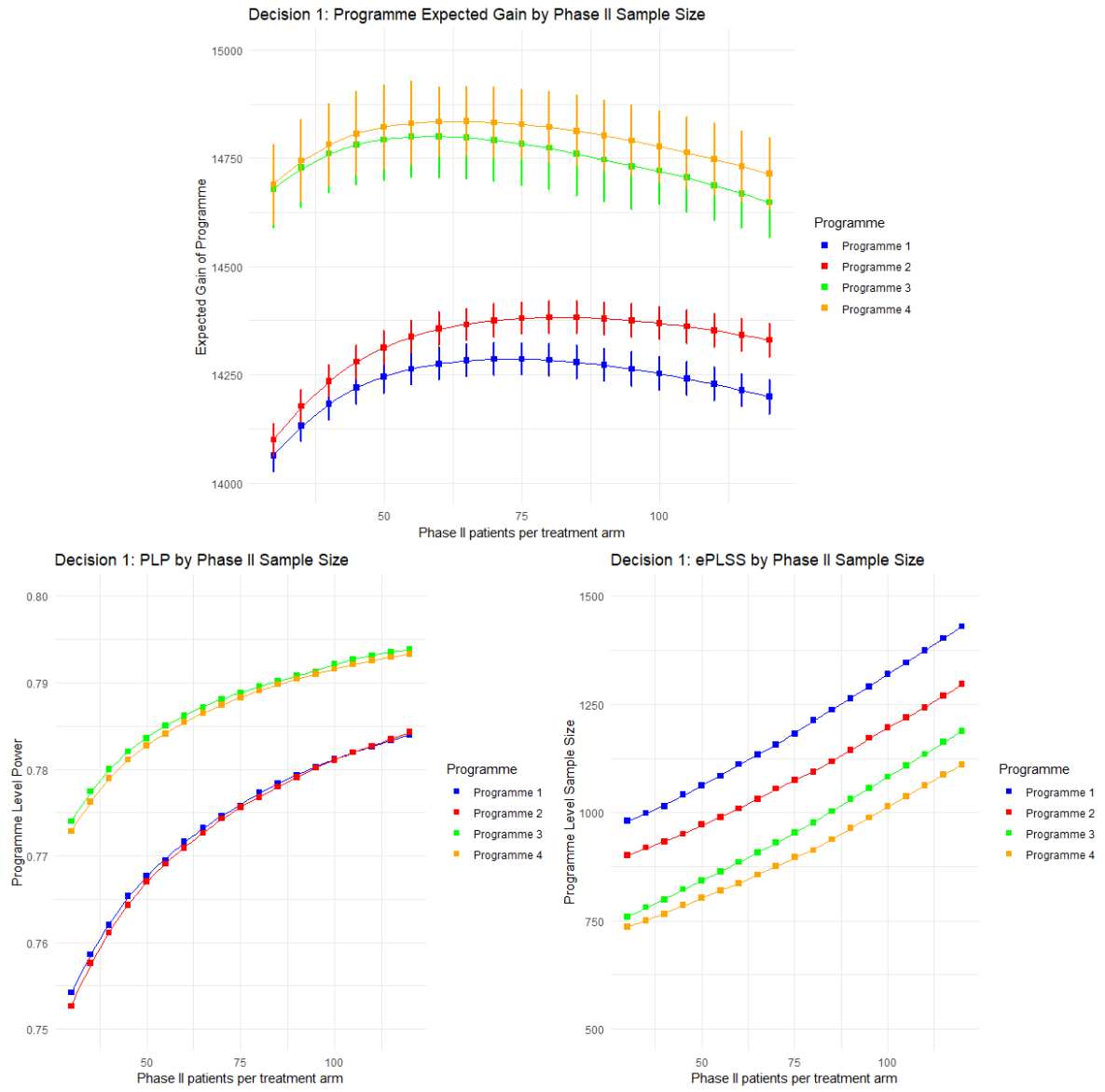

Figure 3-2: *Top:* Expected gain evaluated for different $n_1^{(t)}$ for each programme. The error bars indicate the 95% confidence intervals of each point estimate. Due to coupling, the standard error of the difference between the expected gain of two programmes and the difference between different $n_1^{(t)}$ values of the same programme are very small (at most 20). *Bottom:* Programme level power and expected sample size evaluated for different values of $n_1^{(t)}$ for each programme.

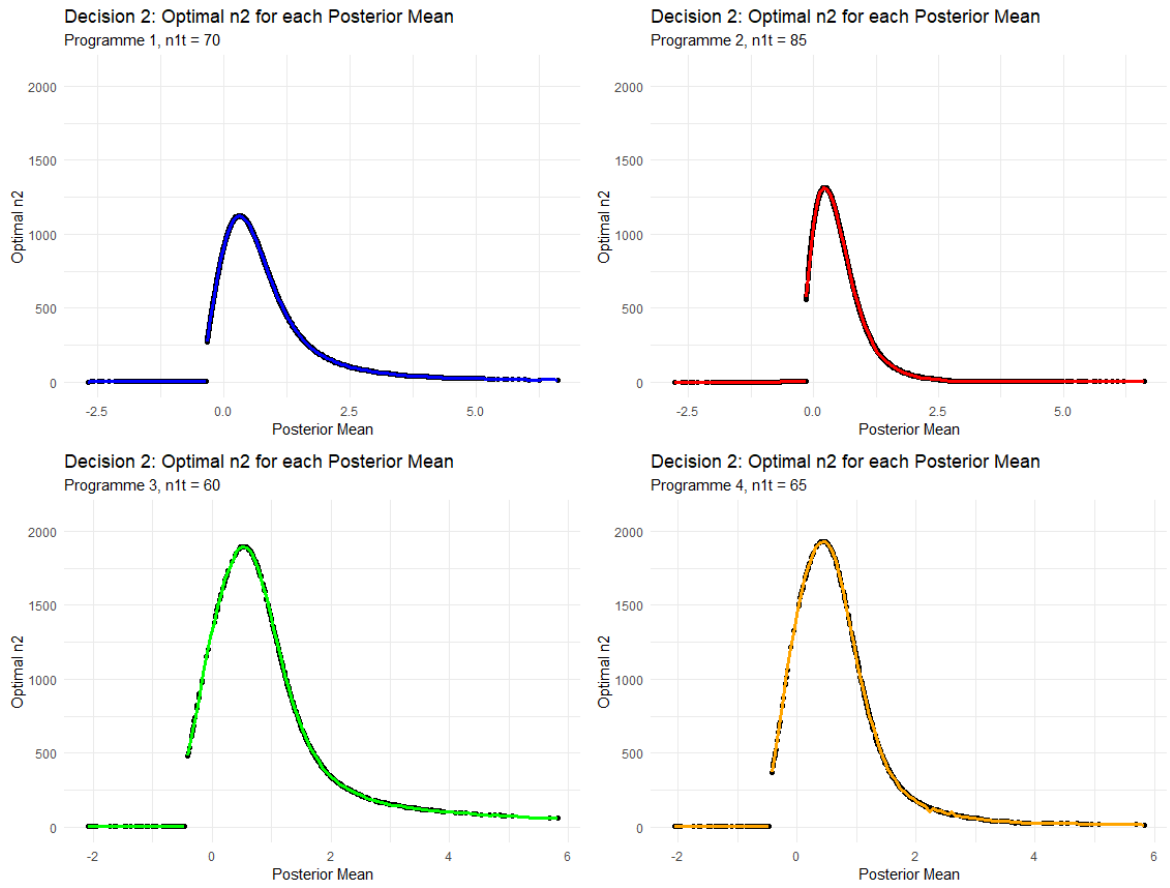

Figure 3-3: Optimal decision rule curves in Decision 2: Optimal choices of n_2 given the posterior mean.

Specifying the weights in the combination test

The weights of the combination test must be adequately specified in order to maximise the expected gain of the programme. A requirement of the combination test is that the weights are specified in advance. However the sample size of Phase III depends upon the Phase II data so it not a-priori known. Therefore the choice of the weights becomes a trade-off to maximise the use of the data from both phases, taking into account the likely sample sizes in each phase.

One must optimise the weights in order to fairly compare a programme with a combination test to another programme. In this study, we have optimised the weights in Programmes 2 and 4 by finding the weights which maximised the expected gain of the programme when one makes optimal decisions at Decision 1 and 2. These weights lend more importance to the Phase III p-value which is generally based upon a larger sample size.

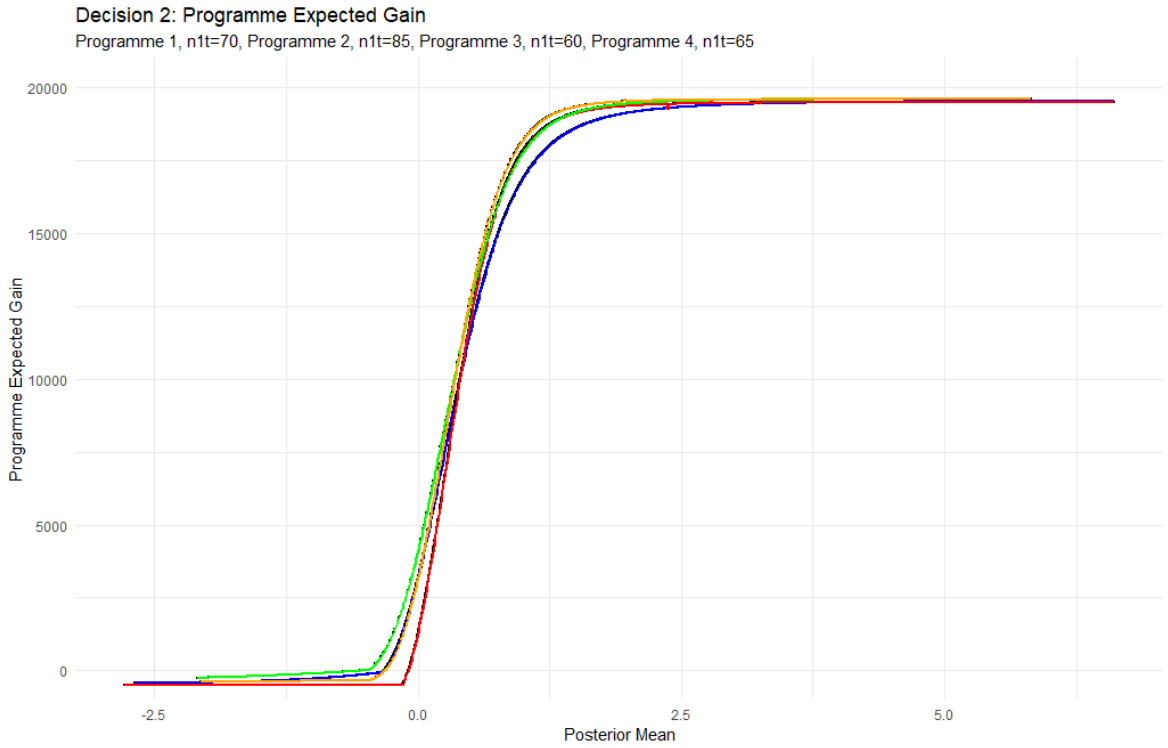

Figure 3-4: The expected gain of the programme in Decision 2 as the posterior mean varies, for each programme with the same colours as in Figure 3-3.

The added value from using combination tests and GSDs

Incorporating combination tests and group sequential designs both add value to a programme (Programmes 2 and 3 versus 1), with group sequential methods adding comparatively more value than combination tests. Using combination test methods in a programme which already has a group sequential Phase III (Programme 4) adds some further value.

On a relative scale, the expected gain from each programme are all fairly similar in the 14,000s. The design of the programme cannot affect the underlying efficacy of the treatments entering it, which accounts for most of the gain. If treatments have a higher treatment effect, then they are more likely to have a successful Phase III. On the other hand, a programme which uses the data in an efficient manner to make decisions (such as the later programmes) saves hundreds of units compared to one which does not (such as Programme 1). Given that each unit is the cost of treating a patient, which may be as much as \$20,000, this is a large saving to the sponsor. Furthermore, a more efficient programme which requires fewer patients to achieve the same information can be considered more ethical. Programme 4 requires 28% fewer patients on average across the programme than Programme 1 as shown in Table 3.2.

Optimal decisions in Decision 2

In Figure 3-3, we are shown the optimal choice of Phase III sample size n_2 as a function of the posterior mean of the treatment effect of treatment i^*. Because of the choice of prior (see Section 3.6.1 for a discussion about the choice of prior), the optimal n_2 is a function only of the posterior mean of the treatment effect of treatment i^*.

The optimal decision curves follow the same shape for each programme. This involves starting at $n_2 = 0$ (that is, not performing a Phase II trial and progression straight to Phase III) for

low values of the posterior mean, before discontinuously jumping to a positive finite value and increasing to a maximum before decreasing and tending towards $n_2 = 0$ again. In Appendix 3.A, we explain the shape of this optimal decision curve.

For programmes with combination tests (Programmes 2 and 4), the hypothesis test depends upon the Phase II data which also determine the posterior mean. Therefore data which produces a low posterior mean will make it more difficult to reject the null hypothesis in the combination test, whilst the opposite is true for data with a large posterior mean. Therefore the optimal decision curve will be narrower in the sense that the jump occurs for a larger value of the posterior mean and the curve decreases for lower values of the posterior mean, which is what we observe in Figure 3-3.

For programmes with group sequential designs in Phase III, the choice of n_2 in Decision 2 is higher as one would expect to stop early in many cases before n_2 patients have been created.

Optimal decisions in Decision 1

The optimal Phase II sample size increases when combination test techniques are implemented, and decreases when group sequential designs are implemented as shown in Table 3.2 and Figure 3-2. If Phase II data can be used in the final hypothesis test via a combination function, it has more value than being simply used to select an appropriate treatment. Therefore it makes sense to use more patients in this phase. Group sequential trials are able to perform well regardless of the size of the treatment effect as the stopping rule adapts to the treatment effect. Therefore group sequential trials are a good choice of design when there is a large amount of uncertainty about the treatment effect.

As shown in Figures 3-2, the optimal set-up and properties of each programme change depending on which statistical techniques are implemented. When combination test techniques are used (Programmes 2 and 4 versus 1 and 3), the optimal setup has a slightly lower programme level power but significantly lower expected programme level sample size. Adding group sequential techniques (Programmes 3 and 5 versus 1 and 2) gives the optimal setup a slightly higher programme level power and lower expected programme level sample size. This is because it becomes viable to perform Phase III trials when there is still a large amount of uncertainty as to whether the treatment effect is positive due to the early stopping rules, and these early stopping rules reduce the average number of patients needed in Phase III.

3.5 A second example: changing the gain function

The gain function proposed in Equation 3.2 is a very simplistic way of quantifying the net present value (NPV) of a drug development programme. In reality, decisions need to be taken which depend upon things such as the treatment effect of the drug, patent life, the time taken to perform Phase II and III, and the costs of setting up marketing.

In this section, we stipulate changes to the gain function to more accurately model the NPV of a programme. The first change we make is to allow the revenue to depend upon the magnitude of the treatment effect of the drug that is marketed. The second change we consider is to make the gain function more closely resemble a financial model as introduced in Section 1.6.2.

3.5.1 Two gain function extensions

New Gain Function A: Revenue dependent upon the treatment effect

In our first change to the gain function, we alter the definition of ζ as specified in Equation 3.2. In the previous case studies, this function was taken to be 1 across its entire domain. We change this to reflect the increased revenue one might expect from finding a treatment with a higher treatment effect, and decreasing the revenue from treatments which are only marginally better than placebo.

In this case study, we use the identity function for ζ. That is, we let

$$\zeta(\theta_{i^*}) = \theta_{i^*}. \tag{3.5}$$

Simulation Result: New Gain Function A

In the case when $\zeta(\theta_{i^*}) = \theta_{i^*}$, the new versions of Figures 3-2 and 3-3 are Figures 3-5 and 3-6.

We note from Figure 3-5 that the overall expected gain for each programme is a lot higher than in the case when $\zeta(\theta_{i^*}) = 1$ (Figure 3-2). This is because when $\theta_{i^*} > 1$, the gain can be potentially a lot higher than before. Particularly as the prior distribution stipulates each $\theta_i \sim N(0, 3)$. Therefore the absolute gains are not particularly comparable to each other. We also note that the order of the programmes that give the highest expected gain is preserved, but the relative difference in expected gain between the programmes is reduced. This is because the main contribution to the expected gain of a programme in this new case comes from high underlying treatment effects, and realisations of programmes with large treatment effects are very likely to be successful, regardless of whether the programme has adaptive elements. In particular, in the $\zeta(\theta_{i^*}) = 1$ case, additional value was brought by increasing the programme level power for small positive true treatment effects, whilst in the $\zeta(\theta_{i^*}) = \theta_{i^*}$ case, these account for less value.

In Figure 3-6, one can see the maximum optimal n_2 across all posterior means is less than in the $\zeta(\theta_{i^*}) = 1$ case in Figure 3-3. As mentioned above, this is due to the lack of desire to power to the same extent as before the realisations when the posterior mean is small but positive, as these realisations now have less value in the $\zeta(\theta_{i^*}) = \theta_{i^*}$ case. For example, the optimal n_2 given a posterior mean of 0.5 is 1200 in the $\zeta(\theta_{i^*}) = 1$ case and 700 in the $\zeta(\theta_{i^*}) = \theta_{i^*}$ case. This difference highlights the need to adequately specify the gain function according to the value different trial conclusions have to the sponsor, as small changes in this specification can significantly change the optimal decision rules. The differences between the optimal decision curves of each programme are similar to the previous case in Figure 3-3.

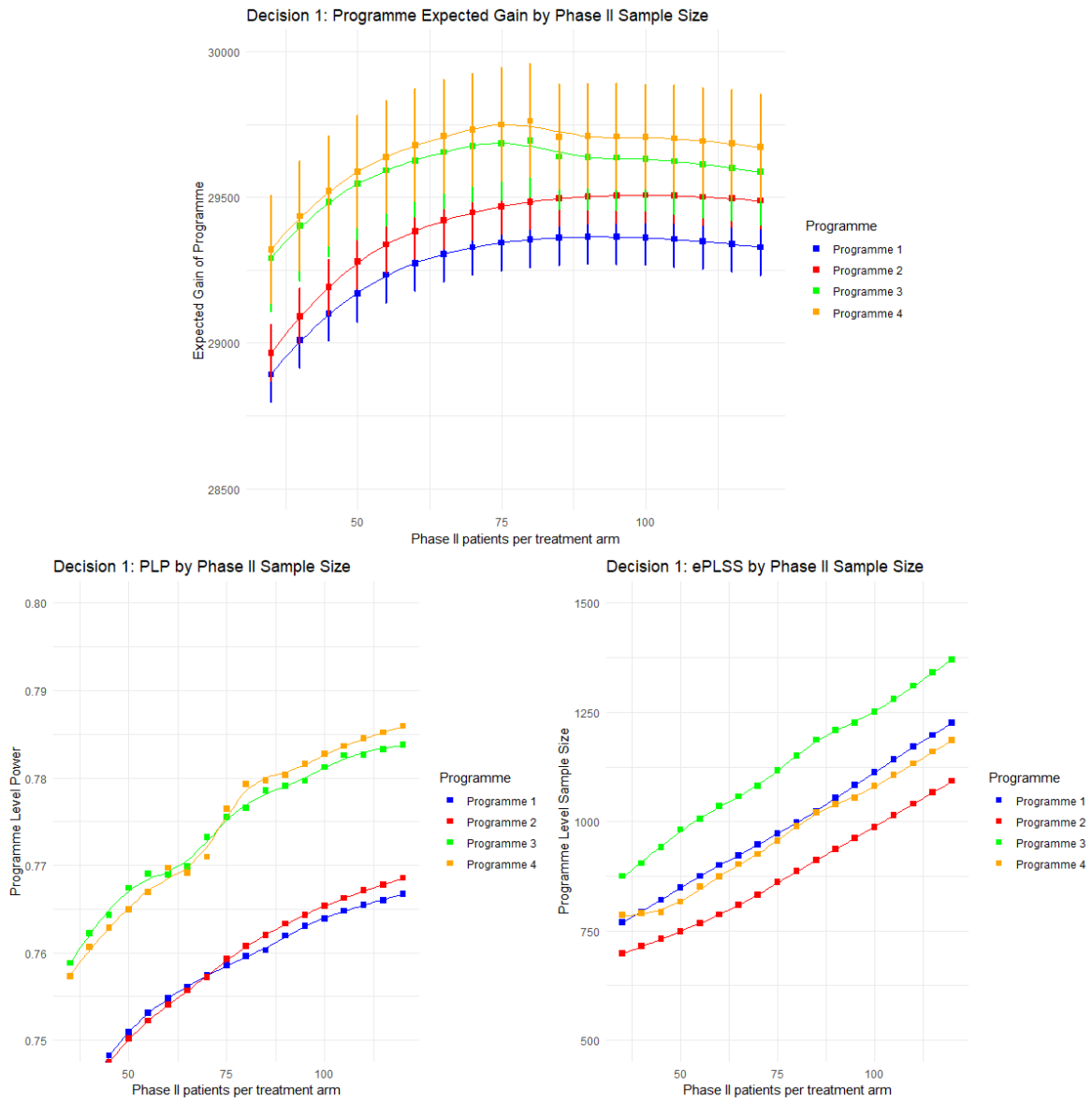

Figure 3-5: *Top:* Expected gain evaluated for different values of Phase II sample size $n_1^{(t)}$ for each programme. The error bars indicate the 95% confidence intervals of each point estimate. Note that due to coupling, the standard error of the difference between the expected gain of two programmes and the difference between different $n_1^{(t)}$ values of the same programme are very small (less than 20). *Bottom:* Programme level power and expected sample size evaluated for different values of Phase II sample size $n_1^{(t)}$ for each programme.

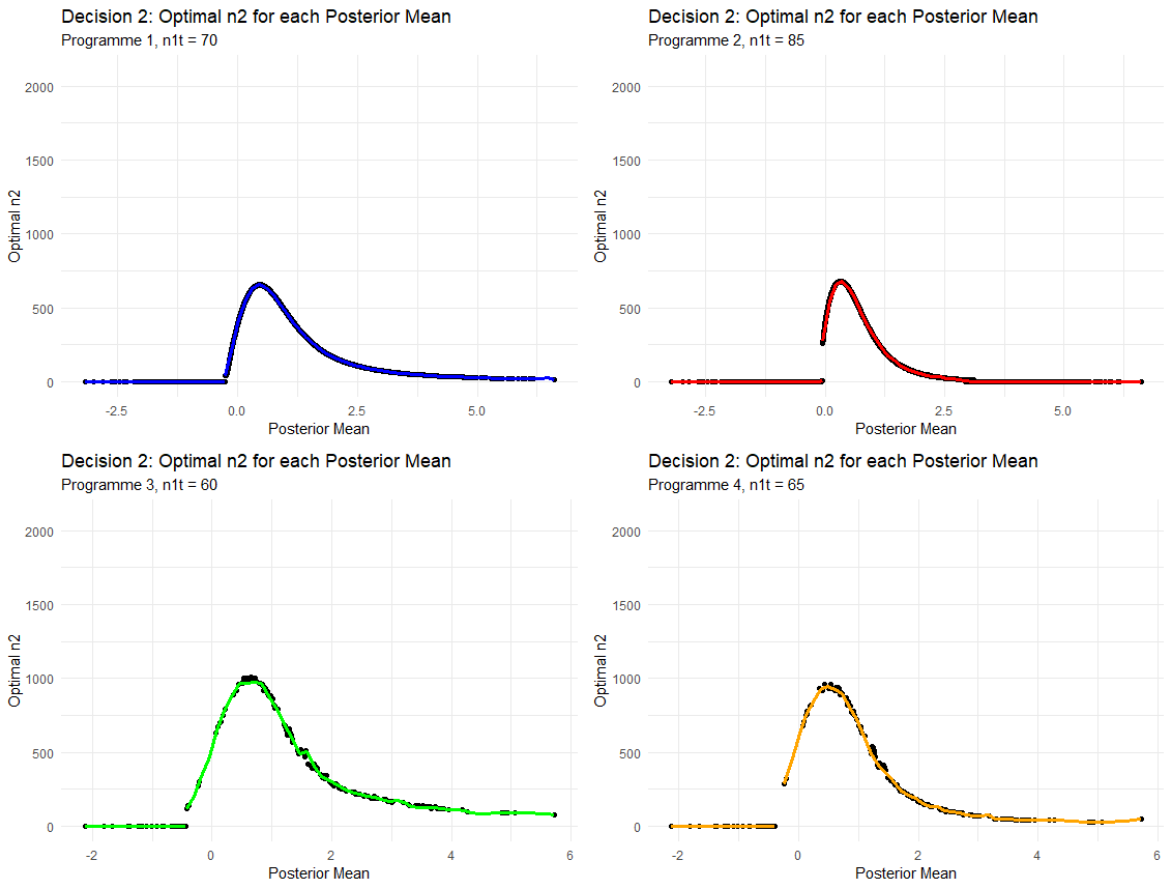

Figure 3-6: Optimal decision rule curves for Decision 2

New Gain Function B: Financial model gain function

The second gain function we consider aims to more accurately model the financial aspect of the decision making in drug development.

We denote n_{phII} and n_{phIII} as the total Phase II and III sample sizes respectively, so $n_{\text{phII}} = Kn_1^{(t)} + n_1^{(c)} = \sqrt{K}(1+\sqrt{K})n_1^{(t)}$ and $n_{\text{phIII}} = 2n_2$.

We define the following parameters for use in the financial model gain function:

$f_{\textbf{phII}}$	Fixed cost for starting Phase II ($ M).
$f_{\textbf{phIII}}$	Fixed cost for starting Phase III ($ M).
$c_{\textbf{phII}}$	Cost per patient for Phase II ($ M).
$c_{\textbf{phIII}}$	Cost per patient for Phase III ($ M).
$\lambda_{\textbf{phII}}$	Patient recruitment rate for Phase II.
$\lambda_{\textbf{phIII}}$	Patient recruitment rate for Phase III.
ρ	Discount rate.
F	Fixed cost to set up marketing ($ M).
R	Monthly revenue from marketed drug ($ M).

$t_{\textbf{phII setup}}$ Time to set up Phase II.

$t_{\textbf{phII trt}}$ Time to treat 1 patient in Phase II.

$t_{\textbf{phIII setup}}$ Time to set up Phase III.

$t_{\textbf{phIII trt}}$ Time to treat 1 patient in Phase III.

$t_{\textbf{mark setup}}$ Time to set up marketing for the drug.

$t_{\textbf{pat}}$ Time until patent expiry starting from the beginning of Phase II set up.

We define the following times

$$\begin{aligned} t_1 &= t_{\text{phII setup}} \\ t_2 &= t_1 + n_{\text{phII}}/\lambda_{\text{phII}} \\ t_3 &= t_2 + t_{\text{phII trt}} \\ t_4 &= t_3 + t_{\text{phIII setup}} \\ t_5 &= t_4 + n_{\text{phIII}}/\lambda_{\text{phIII}} \\ t_6 &= t_5 + t_{\text{phIII trt}} \\ t_7 &= t_6 + t_{\text{mark setup}}. \end{aligned} \tag{3.6}$$

The NPV in the case when the treatment is not successful in Phase III may be written as

$$\begin{aligned} NPV_{\text{NOMARKET}} = &- f_{\text{phII}} \\ &- c_{\text{phII}}\lambda_{\text{phII}} \int_{t_1}^{t_2} e^{-\rho t} dt \\ &- f_{\text{phIII}} e^{-\rho t_3} \mathbb{1}_{(n_{\text{phIII}}>0)} \\ &- c_{\text{phIII}}\lambda_{\text{phIII}} \int_{t_4}^{t_5} e^{\rho t} dt. \end{aligned} \tag{3.7}$$

In the case when the treatment is successful, we write

$$\begin{aligned} NPV_{\text{MARKET}} = NPV_{\text{NOMARKET}} \\ - Fe^{\rho t_6} \\ + R \int_{t_7}^{t_{\text{pat}}} e^{-\rho t} dt. \end{aligned} \tag{3.8}$$

The gain function for this formulation can be written as

$$\mathcal{G}(\mathfrak{I}_2) = NPV_{\text{MARKET}}\ \mathbb{1}_{\{H_{i^*} \text{ is rejected}\}} + NPV_{\text{NOMARKET}}\ \mathbb{1}_{\{H_{i^*} \text{ is not rejected}\}}. \tag{3.9}$$

A schematic for this model is given in Figure 3-7.

We perform another simulation study, using the same inputs and parameters as before with the new gain functions listed above. In the following section, we describe the results of this simulation study.

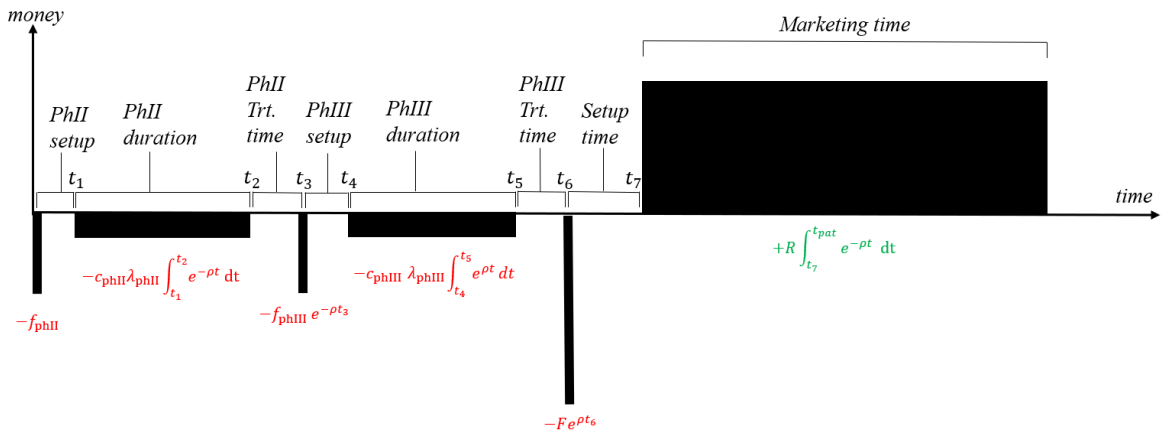

Figure 3-7: Schematic for the financial model for Phase II/III programmes.

Simulation Results: New Gain Function B

We use the following parameters for the simulation study:

f_{phII}	\$ 0.1 M	λ_{phIII}	100 pat/month	$t_{\text{phIII trt}}$	0.5 months
f_{phIII}	\$ 1 M	ρ	0.05	$t_{\text{phII setup}}$	2 months
c_{phII}	\$ 0.012 M	F	\$ 50 M	$t_{\text{phIII setup}}$	2 months
c_{phIII}	\$ 0.008 M	R	\$ 100 M	$t_{\text{mark setup}}$	6 months
λ_{phII}	80 pat/month	$t_{\text{phII trt}}$	0.5 months	t_{pat}	150 months

As before, we compute the optimal decision rules for each programme and compare their performance.

Optimal decisions in Decision 1

Compared to Figures 3-2 and 3-5, Figure 3-8 shows a similar shape of the optimal decision rules over the Phase II sample size. However the optimal Phase II sample size is far lower than in the previous simulation studies, with $n_1^{(t)} = 18$ being approximately optimal for the programmes. There are many new parameters that could be having various effects. In particular the time aspect of the financial model gain function, where finishing the programme earlier is rewarded far more in the sense that one can market the drug for longer until the patent expires, giving a larger gain.

Optimal decisions in Decision 2

Compared to Figures 3-3 and 3-6, Figure 3-9 shows similar shapes to the previous simulation studies. Comparisons regarding the absolute numbers for the decision rules are not sensible due to the different gain function. The Phase III patient cost is less than the Phase II patient cost meaning the optimal programme favours more patients in Phase III compared to Phase II.

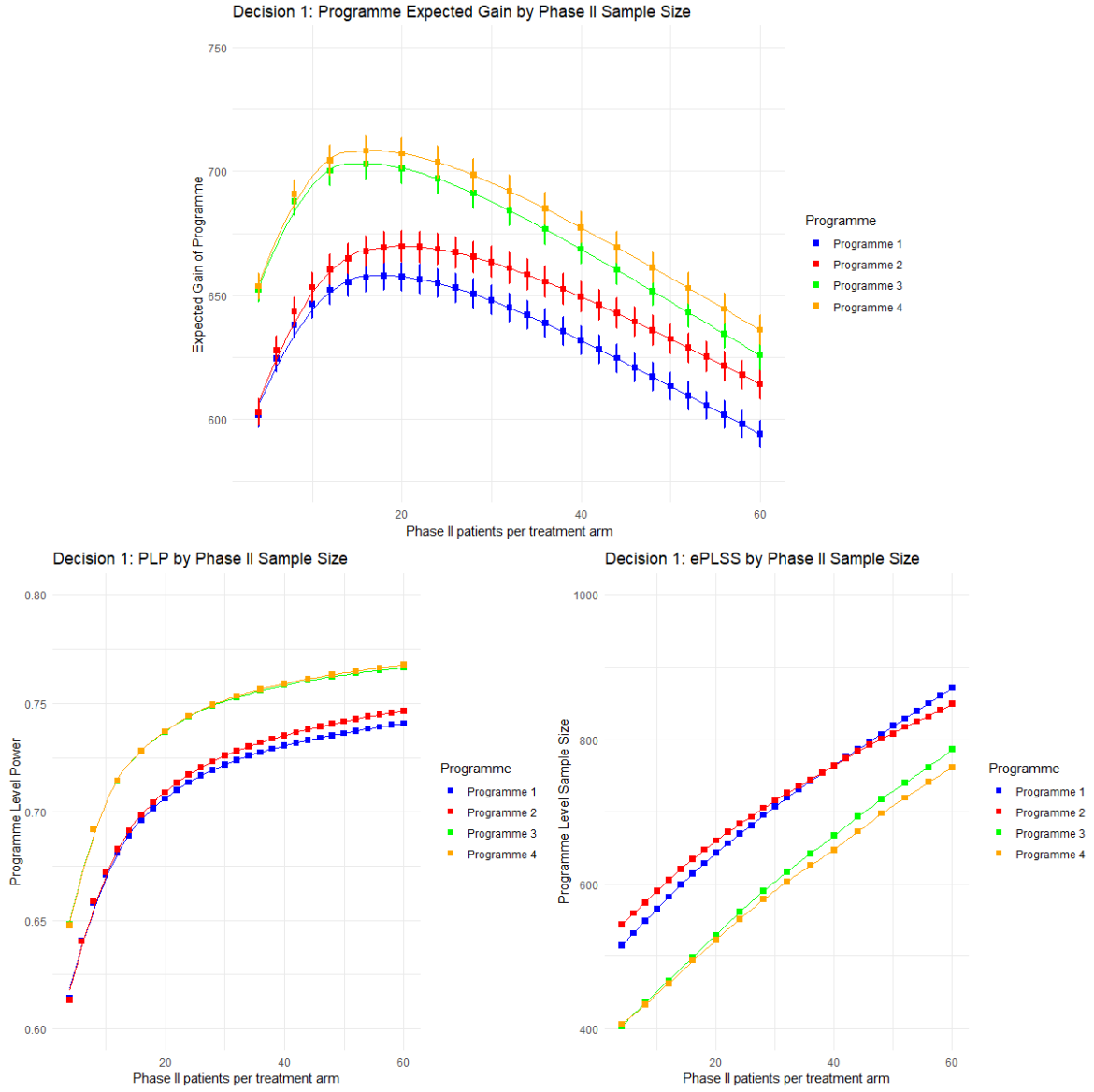

Figure 3-8: *Top:* Expected gain evaluated for different values of Phase II sample size $n_1^{(t)}$ for each programme. The error bars indicate the 95% confidence intervals of each point estimate. Note that due to coupling, the standard error of the difference between the expected gain of two programmes and the difference between different $n_1^{(t)}$ values of the same programme are very small (below 20). *Bottom:* Programme level power and expected sample size evaluated for different values of Phase II sample size $n_1^{(t)}$ for each programme.

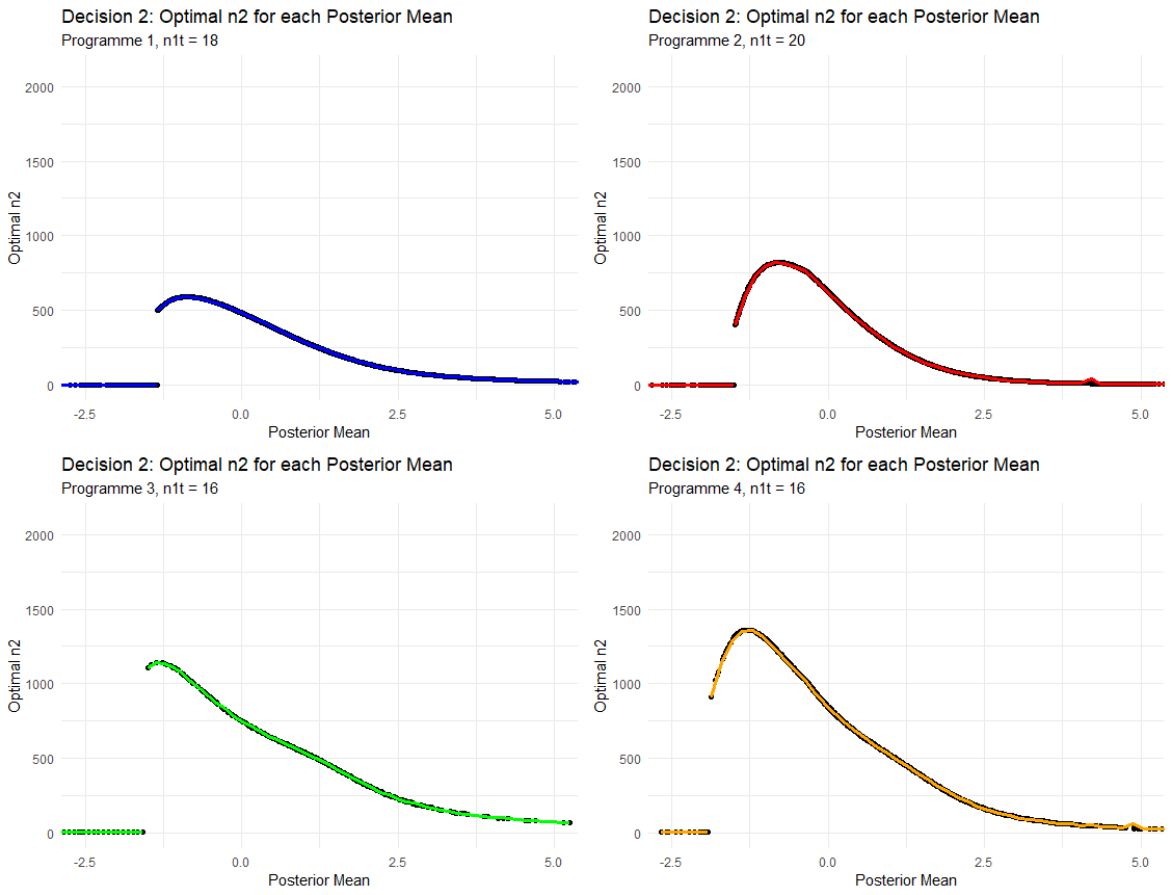

Figure 3-9: Optimal decision rule curves in Decision 2.

3.5.2 Simulation study conclusions

In Sections 3.4 and 3.5, we have performed simulation studies to compute the optimal decision rules for some examples of a Phase II/III programme. We have shown that this framework may be applied with different gain functions specifying the value of different outcomes of the programme to the sponsor. In particular, one may compare different approaches for performing the programme, including utilising group sequential methods or combination tests. These comparisons may be done fairly if each programme is individually optimised with respect to its decision rules. In conclusion, this framework provides a tool one may use for ones own drug development programme situation using ones own numbers relating to the revenue, cost of treating a patient, and priors on the treatment effect.

In these simulation studies, we evaluated the value to the programme of utilising group sequential methods and combination tests. It was found that group sequential methods brought a large amount of value to the programme. This came from the usual benefits of a group sequential design of having lower expected sample size, in addition to allowing a smaller Phase II sample size due to the group sequential design performing well when there is a large amount of uncertainty as to the true treatment effect. The use of combination testing in the portfolio added a smaller amount of value to the programmes, mostly through reducing the sample size of Phase III required in order to achieve the same power. It is for the investigator to deduce whether the additional value each of these techniques bring to the

programme are worth it compared to any logistical challenges they may also bring.

3.6 Priors, distributions, and computing the optimal decision rules details

In this section, we provide more details on an appropriate specification of a prior on the treatment effects, derive the distribution of densities and optimal decision rules, and discuss the computations of these decision rules.

3.6.1 Prior specification

The specification of the prior is an important aspect of the model, as this specifies the treatment effects one may expect to enter the programme. Changes in prior beliefs may change the optimal decision rules within the programme and the corresponding programme value.

For computational and interpretability reasons, using a multivariate Gaussian prior is the common approach. We assume a prior distribution for θ of the form

$$\boldsymbol{\theta} \sim N(\boldsymbol{\theta}_0, \Sigma_0). \tag{3.10}$$

1. Independent Multivariate Normal Prior

Here, $\boldsymbol{\theta}_0$ is a vector of length K, Σ_0 is a $K \times K$ diagonal matrix.

This prior assumes each treatment effect to be independent and normally distributed.

2. Dependent Multivariate Normal Prior

Here, $\boldsymbol{\theta}_0$ is a vector of length K, and Σ_0 is a $K \times K$ matrix with at least one non-diagonal entry non-zero.

This prior assumes the treatment effects are dependent and normally distributed.

3. *Special Prior 1*

$\boldsymbol{\theta}_0$ is arbitrary and Σ_0 some multiple of

$$[\Sigma_0]_{i,j} = \begin{cases} 1 & \text{if } i = j \\ (1+\sqrt{K})^{-1} & \text{if } i \neq j \end{cases}. \tag{3.11}$$

This prior is designed so that the posterior distribution of the treatment effects has special properties. In particular, the mean of the posterior distribution of the treatment effect of treatment i^* depends only on the Phase II data from that treatment, namely $\hat{\theta}_{i^*,1}$, and no other element of $\hat{\boldsymbol{\theta}}_1$. We prove this in Appendix 3.B.

In certain settings, other prior distributions may be more appropriate. Chapter 4 deals with dose response models such as an Emax model with a prior on model parameters, and we report a simulation study comparing this approach with one that uses a dependent multivariate normal prior (Prior 2). Chapter 6 deals with simple discrete priors in a more complex problem.

3.6.2 Programme distribution derivations

Suppose that the prior for the treatment effect for each drug is specified as $\boldsymbol{\theta} \sim N(\boldsymbol{\mu}_0, \Sigma_0)$. We derive the distributions of the maximum likelihood estimates of the treatment effect vector $\boldsymbol{\theta}$ as well as the posterior distribution for each θ_i given the Phase II data.

Recall from Section 3.3.2, $n_1^{(c)}$ is chosen from $n_1^{(t)}$ such that equation $n_1^{(c)} = \sqrt{K} n_1^{(t)}$ holds.

Define

$$\mathcal{I}_1 = \frac{n_1^{(t)}}{\sigma^2}(1 + K^{-1/2})^{-1} \tag{3.12}$$

and

$$\Sigma = \begin{pmatrix} \mathcal{I}^{-1} & \sigma^2 K^{-1/2}/n_1^{(t)} & \dots & \sigma^2 K^{-1/2}/n_1^{(t)} \\ \sigma^2 K^{-1/2}/n_1^{(t)} & \mathcal{I}^{-1} & & \vdots \\ \vdots & & \ddots & \sigma^2 K^{-1/2}/n_1^{(t)} \\ \sigma^2 K^{-1/2}/n_1^{(t)} & \dots & \sigma^2 K^{-1/2}/n_1^{(t)} & \mathcal{I}^{-1} \end{pmatrix}, \tag{3.13}$$

where $\mathcal{I}$ is the information observed per treatment in Phase II.

Then the sampling distributions of the vector of maximum likelihood estimates from the Phase II data given $\boldsymbol{\theta}$ is

$$\hat{\boldsymbol{\theta}}_1 | \boldsymbol{\theta} \sim N\left(\boldsymbol{\theta}, \Sigma\right). \tag{3.14}$$

As the likelihood and prior are normally distributed, conjugacy easily gives us the posterior distribution of $\boldsymbol{\theta}$,

$$\boldsymbol{\theta} \mid \hat{\boldsymbol{\theta}}_1 \sim N\left((\Sigma_0^{-1} + \Sigma^{-1})^{-1}(\Sigma^{-1}\hat{\boldsymbol{\theta}}_1 + \Sigma_0^{-1}\boldsymbol{\theta}_0) \ , \ (\Sigma_0^{-1} + \Sigma^{-1})^{-1} \right). \tag{3.15}$$

In particular, the posterior distribution of the treatment effect of the ith treatment is

$$\theta_i \mid \mathfrak{I}_1 \sim N\left([(\Sigma_0^{-1} + \Sigma^{-1})^{-1}(\Sigma^{-1}\hat{\boldsymbol{\theta}}_1 + \Sigma_0^{-1}\boldsymbol{\theta}_0)]_i \ , \ [(\Sigma_0^{-1} + \Sigma^{-1})^{-1}]_{ii} \right) \tag{3.16}$$

where one recalls that $\mathfrak{I}_1$ denotes the set of cumulative summary statistics known directly after Phase II, which contains $\hat{\boldsymbol{\theta}}_1$. We use this notation in preparation for Section 3.6.3.

The distributions for the maximum likelihood estimates in Phase III depend on how Phase III is specified. In the simple case, Phase III may have a fixed sample design. Alternatively, it may be group sequential.

In a fixed sample Phase III, the sampling distribution of the maximum likelihood estimate of θ_{i^*} is

$$\hat{\theta}_{2,i^*} \mid \theta_{i^*} \sim N(\theta_{i^*}, 2\sigma^2/n_2), \tag{3.17}$$

and therefore the posterior predictive distribution given $\mathfrak{I}_1$, is

$$\hat{\theta}_{2,i^*} \mid \mathfrak{I}_1 \sim N([(\Sigma_0^{-1} + \Sigma^{-1})^{-1}(\Sigma^{-1}\hat{\boldsymbol{\theta}}_1 + \Sigma_0^{-1}\boldsymbol{\theta}_0)]_i, [(\Sigma_0^{-1} + \Sigma^{-1})^{-1}]_{ii}^2 + 2\sigma^2/n_2). \tag{3.18}$$

3.6.3 Optimal decision rule derivations

In Chapter 1, we defined what it means for decisions to be optimal in a drug development process. In this section, we derive the optimal decision for Decisions 1 and 2 in terms of our notation in a Phase II/III programme.

Decision 2

Decision 2 is the decision made after Phase II has been completed when all the variables in $\mathcal{I}_1$ are known, and decides the Phase III sample size n_2 and the treatment to take forward to Phase III, i^*.

In the most general form, the optimal decision at Decision 2 is to choose n_2 and i^* such that the expected gain given $\mathfrak{I}_1$ is maximised. That is, we choose i^* and n_2 such that the following expression is maximised:

$$\begin{aligned}\mathcal{D}^{(2)}_{i^*,n_2,\mathfrak{I}_1} &:= \mathbb{E}[\ \mathcal{G}(\mathfrak{I}_2,\theta_{i^*}) \mid \mathfrak{I}_1,\ n_2,\ i^*] \\ &= \int_{\mathbb{R}} \mathbb{E}\left[\ \mathcal{G}(\mathfrak{I}_2,\theta_{i^*}) \mid \mathfrak{I}_1,\theta_{i^*},n_2\ ,i^*\ \right]\pi_{\theta_{i^*}|\mathfrak{I}_1}(\theta_{i^*}|\mathfrak{I}_1)\ d\theta_{i^*},\end{aligned} \tag{3.19}$$

where $\pi_{\theta_{i^*}|\mathfrak{I}_1}$ is the posterior density of θ_{i^*} given $\mathfrak{I}_1$ as in Equation 3.16. The integral in 3.19 is clearly maximised by the i^* which has the largest posterior mean, regardless of the choice of n_2. Therefore define i^* as the treatment which gives the largest posterior mean, which is given by

$$i^* := \underset{i}{\text{argmax}}[(\Sigma_0^{-1}+\Sigma^{-1})^{-1}(\Sigma^{-1}\hat{\boldsymbol{\theta}}_1+\Sigma_0^{-1}\boldsymbol{\theta}_0)]_i, \tag{3.20}$$

using Equation 3.16.

We may express $\mathcal{D}^{(2)}_{n_2,\mathfrak{I}_1}$ in two ways, by conditioning on the posterior mean and Phase III likelihood respectively:

$$\mathcal{D}^{(2)}_{n_2,\mathfrak{I}_1} = \int_{\mathbb{R}} \mathbb{E}\left[\ \mathcal{G}(\mathfrak{I}_2,\theta_{i^*}) \mid \mathfrak{I}_1,\theta_{i^*},n_2\ \right]\pi_{\theta_{i^*}|\mathfrak{I}_1}(\theta_{i^*}|\mathfrak{I}_1)\ d\theta_{i^*}, \tag{3.21}$$

or

$$\mathcal{D}^{(2)}_{n_2,\mathfrak{I}_1} = \int_{\mathbb{R}} \mathbb{E}\left[\ \mathcal{G}(\mathfrak{I}_2,\theta_{i^*}) \mid \mathfrak{I}_1,\hat{\theta}_{2,i^*},n_2\ \right]\pi_{\hat{\theta}_{2,i^*}|\mathfrak{I}_1}(\hat{\theta}_{i^*}|\mathfrak{I}_1)\ d\hat{\theta}_{2,i^*}, \tag{3.22}$$

where $\pi_{\hat{\theta}_{2,i^*}|\mathfrak{I}_1}$ is the probability density function of the posterior predictive distribution of the maximum likelihood estimate of θ_{i^*} in Phase III given $\mathfrak{I}_1$ given in Equation 3.18.

We write

$$\mathcal{D}^{(2)}_{\mathfrak{I}_1} := \max_{n_2} \mathcal{D}^{(2)}_{n_2,\mathfrak{I}_1} \tag{3.23}$$

for the expected gain resulting from an optimal choice of n_2.

The calculation of Equation 3.23 depends upon whether Phase III is group sequential or not, and whether the gain function depends explicitly on the treatment effect (that is, whether ζ in Equation 3.2 is a function of θ_{i^*} or not). It is computationally convenient to use Equation 3.22

when the gain function is not explicitly dependent on the treatment effect, and Equation 3.21 otherwise. We illustrate the calculation in the different cases below.

Phase III is fixed sample and the gain function is not explicitly dependent on the treatment effect

The density for the Phase III maximum likelihood estimate is available from Equation 3.18, so the integral in Equation 3.22 may be reduced to a weighted sum of two probabilities of having a $\hat{\theta}_{2,i^*}$ high enough to reject H_{i^*}, and not. In the case when it is not, the gain may be negative due to the cost of treating patients.

Phase III is fixed sample and the gain function is explicitly dependent on the treatment effect

The posterior distribution for the treatment effect given the Phase II data is available from Equation 3.16. The expected gain given a treatment effect θ_{i^*} and Phase II data $\mathfrak{I}_1$ can be found using the conditional probability of rejection found using the properties of the Phase III trial. One uses Equation 3.21 using the numerical integration method described in Section 1.6.1.

Phase III is group sequential

When Phase III is group sequential, one may use a different method of calculation.

The expected gain term in Equation 3.21 becomes a nested multivariate integral of the statistics at each analysis in the group sequential design. The outer integral in terms of θ_{i^*} can be moved inside to be the innermost integral, which leads to a more efficient calculation. In Appendix 3.C, we describe this approach in detail.

Decision 1

Decision 1 is the decision made before Phase II commences, which chooses the number of patients for Phase II. We choose $n_1^{(t)}$ only since $n_1^{(c)}$ is found from the relation $n_1^{(c)} = \sqrt{K} n_1^{(t)}$.

We find the $n_1^{(t)}$ to maximise the expected gain given $\mathfrak{I}_0$,

$$\mathcal{D}^{(1)}_{n_1^{(t)},\mathfrak{I}_0} = \mathbb{E}[\mathcal{G}(\mathfrak{I}_2, \theta_{i^*}) | \mathfrak{I}_0, n_1^{(t)}]. \tag{3.24}$$

We may condition on the treatment effect vector $\boldsymbol{\theta}$ and the the maximum likelihood estimate from the Phase II data $\hat{\boldsymbol{\theta}}_1$ to write Equation 3.24 in terms of the expected gain given optimal decisions in Decision 2, $\mathcal{D}^{(2)}_{\mathfrak{I}_1}$:

$$\begin{aligned}
\mathcal{D}^{(1)}_{n_1^{(t)},\mathfrak{I}_0} &= \int_{\mathbb{R}^K}\int_{\mathbb{R}^K} \mathbb{E}\left[\ \mathcal{G}(\mathfrak{I}_2, \theta_{i^*}) \mid \mathfrak{I}_0, \hat{\boldsymbol{\theta}}_1,\ n_1^{(t)}\right] \pi_{\hat{\boldsymbol{\theta}}_1}(\hat{\boldsymbol{\theta}}_1 \mid n_1^{(t)}, \boldsymbol{\theta})\ \pi_{\boldsymbol{\theta}}(\boldsymbol{\theta})\ d\hat{\boldsymbol{\theta}}_1\ d\boldsymbol{\theta} \\
&= \int_{\mathbb{R}^K}\int_{\mathbb{R}^K} \mathbb{E}\left[\ \mathcal{G}(\mathfrak{I}_2, \theta_{i^*}) \mid \mathfrak{I}_1\right] \pi_{\hat{\boldsymbol{\theta}}_1}(\hat{\boldsymbol{\theta}}_1 \mid n_1^{(t)}, \boldsymbol{\theta})\ \pi_{\boldsymbol{\theta}}(\boldsymbol{\theta})\ d\hat{\boldsymbol{\theta}}_1\ d\boldsymbol{\theta} \\
&= \int_{\mathbb{R}^K}\int_{\mathbb{R}^K} \mathcal{D}^{(2)}_{\mathfrak{I}_1}\ \pi_{\hat{\boldsymbol{\theta}}_1}(\hat{\boldsymbol{\theta}}_1 \mid n_1^{(t)}, \boldsymbol{\theta})\ \pi_{\boldsymbol{\theta}}(\boldsymbol{\theta})\ d\hat{\boldsymbol{\theta}}_1\ d\boldsymbol{\theta}.
\end{aligned} \tag{3.25}$$

This integral is difficult to compute using numerical integration due to the large number of dimensions of each of the integration variables. A Monte Carlo approach is therefore preferred

for evaluating the integral by multiple forward simulations of the Phase II/III programme. Quantifying the Monte Carlo error is straightforward.

Let $\hat{\boldsymbol{\theta}}^{(n)} \overset{\text{iid}}{\sim} \hat{\boldsymbol{\theta}}_1 \mid n_1^{(t)}, \boldsymbol{\theta}^{(n)}$ (the distribution of the maximum likelihood estimates in Phase II) where $\boldsymbol{\theta}^{(n)} \overset{\text{iid}}{\sim} \boldsymbol{\theta} \mid \mathfrak{I}_0$ (the prior distribution for the treatment effect), both for $n = 1, ..., N$. The Monte Carlo estimate takes the form

$$\mathcal{MC}^{(1)}_{n_1^{(t)},\mathfrak{I}_0} := \frac{1}{N} \sum_{n=1,...,N} \mathcal{D}^{(2)}_{(\mathfrak{I}_0,\hat{\theta}_1^{(n)},n_1^{(t)},n_1^{(c)})}. \tag{3.26}$$

One uses this Monte Carlo approximation to approximate $\mathcal{D}^{(1)}_{n_1^{(t)},\mathfrak{I}_0}$,

$$\mathcal{D}^{(1)}_{n_1^{(t)},\mathfrak{I}_0} \approx \mathcal{MC}^{(1)}_{n_1^{(t)},\mathfrak{I}_0}, \tag{3.27}$$

The optimal decision in Decision 1 is found using these Monte Carlo estimates:

$$\mathcal{D}^{(1)}_{\mathfrak{I}_0} := \max_{n_1^{(t)}} \mathcal{MC}^{(1)}_{n_1^{(t)},\mathfrak{I}_0} \tag{3.28}$$

for the expected gain resulting from an optimal choice of $n_1^{(t)}$ in Decision 1.

3.6.4 Computing the optimal decision rules

In this section, we outline the main dynamic programming algorithms used to calculate the optimal decision rules and note the computational approaches used.

Algorithms

We outline the 3 main functions used to compute the optimal decision rules in the following boxes.

`Dec_1`
- For each $n_1^{(t)}$
  - For each MC simulation as in Equation 3.26:
    - Simulate a programme using `prg_sim`, storing the expected gain.
  - Calculate the mean expected gain from these simulations.
- Identify the $n_1^{(t)}$ with the largest expected gain and return the $n_1^{(t)}$ and expected gain.

`Prg_sim`
- Simulate $\boldsymbol{\theta}$ using the prior distribution as in Section 3.6.1.
- Simulate $\hat{\boldsymbol{\theta}}_1$ using the distribution in Equation 3.14.
- Calculate the optimal i^*, n_2 and corresponding programme expected gain using the `Dec_2` function.
- Return the expected gain.

Dec_2

- Identify i^* using Equation 3.20.
- For each n_2:
  - Calculate expected gain using the methods described in Section 3.6.3.
- Identify the n_2 with the largest expected gain and return the i^*, n_2 and corresponding expected gain.

Computational techniques

In order to reduce the computation time needed to compute the optimal decisions, we use the following techniques described in Section 1.6 with Decision 1 and 2.

Decision 2: Group Sequential Design Computations

As described in Section 3.6.3, in Appendix 3.C we derive an efficient method for calculating the probability of rejection of a Group Sequential Design given a treatment effect is distributed according to a normal distribution.

Decision 1: Coupling

As described in Section 1.6, coupling the errors of successive Monte Carlo estimators can reduce the variance of the difference of the two estimators. Specifically, in Decision 1 we can accomplish this by re-using the same underlying standard normal random variables when simulating variables for Equation 3.26 for different values of $n_1^{(t)}$. When looking at other programmes, these same sets of standard normal random variables can be used to reduce the variance of the difference in expected gain between 2 programmes.

Decisions 1: Use of Splines

The most computationally intensive part of the Decision 1 calculation is the calculation of $\mathcal{D}^{(2)}_{\mathfrak{I}_1(\hat{\boldsymbol{\theta}}_1^{(k)})}$ in Equation 3.26. From Section 1.6.2, if the expected gain of the maximising i^* and n_2 is a function of the posterior mean $\breve{\theta}_{i^*,1}$ only, the spline method may be used to interpolate $\mathcal{D}^{(2)}_{\mathfrak{I}_1(\hat{\boldsymbol{\theta}}_1^{(k)})}$ from $\breve{\theta}_{i^*,1}$, bypassing the need to do a lengthy calculation to evaluate $\mathcal{D}^{(2)}_{\mathfrak{I}_1(\hat{\boldsymbol{\theta}}_1^{(k)})}$ in Equation 3.26. This is the case when the combination function is a function of the Phase III data only or the prior is *Special Prior 1*. When this is not the case, and the expected gain of the maximising i^* and n_2 is a function of both the posterior mean $\breve{\theta}_{i^*,1}$ and the p-value $\tilde{p}_{i^*,1}$, then thin plate splines may be used instead.

3.7 Discussion

The Seamless Phase II/III Programme with Treatment Selection in Current Research

The approach taken in this chapter to model a seamless Phase II/III programme with treatment selection relates to several current research themes in adaptive designs. We describe two themes in this section, and outline how our approach is a special case of each.

Multi Arm Multi Stage Trials

A modification to the gold standard randomised controlled trial design to allow more treatments and stages makes the trial a multi-arm multi-stage (MAMS) trial. Multi-arm means the trial is initialised with several treatments of interest. Multi-stage refers to the trial taking several stages, where interim adaptations may be performed. In general, at the end of each stage, treatments may be dropped according to some pre-specified rule, and the trial continues until either one treatment is deemed superior to control, or the trial is stopped for futility.

Only one control arm is needed to evaluate multiple new treatments meaning the sample size and administrative costs are reduced, and the dropping of underperforming treatments earlier in the study can reduce the expected sample size. The 'Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE)' (James et al. (2009)) trial is one of the first to employ such methodology. The trial contained six treatments with interim analyses used to drop underperforming treatments. Magirr et al. (2012) provided an approach that gave exact numerical computations for the acceptance and rejection boundaries, which can be computed using numerical integration when the number of stages is 4 or less. Wason and Jaki (2012) make an attempt to optimise under this framework to minimise the expected sample size under some restrictions and different optimality criterions.

Magirr et al. (2014) extends the previous framework by using combination tests within closed testing procedures. These allow adaptations to be performed between stages with multiple treatments allowed to continue throughout the stages.

Our approach may then be considered a special case of a general MAMS trial, using combination tests within closed testing procedures to control error rates. In particular, the number of stages will be two, with all but one treatment dropped for the second stage. This follows the traditional process of Phase II and III in drug development with Phase II being concerned with treatment selection and Phase III providing confirmatory evidence of the efficacy of a chosen treatment. These restrictions mean it is easier to optimise the programme to a greater extent than the more general framework.

Seamless Phase II/III Trials

The simplest form of a seamless Phase II/III trial is an operationally seamless Phase II/III trial. Operationally seamless Phase II/III trials aim to reduce the 'white space' between Phase II and III in an operation sense of having a pre-defined decision rule between the two phases. However they do not use Phase II data in the confirmatory hypothesis test. We have presented an inferentially seamless Phase II/III design in this chapter, which refers to the use of Phase II data within the confirmatory hypothesis test at the end of Phase III.

Our approach may be described as a seamless Phase II/III design in both senses as we allow the use of Phase II data in the final analysis whilst additionally specifying a decision rule to choose the design of Phase III based on the Phase II data without a need for any 'white space'.

Inferentially seamless designs in particular have received academic attention in recent years in research. They are proposed in generality in Bretz et al. (2006) and Jennison and Turnbull (2007). The features of these designs are that they allow for multiple treatments in the first stage (corresponding to Phase II) with one or more treatments selected to continue to

the second stage (corresponding to Phase III). Combination functions are used as the final test statistic within a closed testing procedure in order to control the familywise error rate in the strong sense. Jennison and Hampson (2015) work within this seamless Phase II/III framework to identify optimal data combination rules based on assumed treatment effects. In particular, a closed testing procedure using an inverse normal combination rule and a Dunnett test for intersection hypotheses is one of those which is robust in its efficiency under the framework studied.

A Discussion About Our Approach

We presented a framework in which to perform a Phase II/III programme with treatment selection at the interim analysis. Within this framework, we derived optimal decision rules according to Bayesian decision theory with a gain function. We performed several simulation studies to examine the properties of the programmes, and examined the value to the programme of introducing adaptive methods such as allowing the programme to be inferentially seamless, or the use of group sequential designs.

We found that group sequential methods added comparably more to the programme than the use of combination tests to make the programme inferentially seamless. This result held for both simple gain functions, and those that tried to more accurately model the financial impact of decisions in the programme.

The optimal decision rules were found to be dependent upon the type of gain function used, with more complex gain functions incorporating time and treatment effect producing different optimal decision curves in both decision points before Phase II and before Phase III. One should ensure aspects of the decision making process that are important in decision making for a specific programme, such as time until patent expiry or safety concerns, are well accounted for in the gain function.

Strengths of approach

The approach taken here provides a computationally feasible method to studying a complex problem. Many outputs of the approach are interesting in their own right. The framework can comprehensively deal with degrees of beliefs about unknown treatment effects and update these given data.

The approach produces visually intuitive decision curves for Decision 1 and Decision 2 and properties of the optimised programme. By changing the parameters of the treatment effects or the structure of the programme, one can easily assess how the value of the programme changes when these changes occur. In particular, this allowed us to fairly assess the value of bringing adaptive elements to the programme in the form of combination tests and group sequential designs.

A comment on studying the drug development process as a Phase II/III programme

One of the arguments for studying Phase II and III together as a programme is that decisions about the individual phases are interrelated. In particular, the optimal spread of budget between Phase II and III may be found only when considering the programme as a whole, rather than each phase individually.

Suppose one has a portfolio of Phase II/III programmes. One decision one must be required to make is to allocate resources to the programmes in the portfolio. Clearly, here also the

decisions are interrelated, such that the optimal spread of budget will be found only when considering the portfolio as a whole. Fixing the budgets for each programme and optimising them individually may not be optimal. This provides an argument for studying not just individual phases together as a programme, but studying individual programmes together as a portfolio of programmes.

Whilst one should be aware of the wider picture, clearly there is still value in studying phases or programmes in isolation. Studying programmes and portfolios is more difficult than studying individual phases and programmes respectively, which means that simplifying assumptions must be made, which may remove the intricacies of the decision making problem which are interesting to the investigator. In Chapter 6, we make an attempt to generalise our thinking to considering a portfolio of programmes. In that approach, we make the simplification to drop some details and make other simplifying assumptions about each programme within the portfolio. These include considering only Phase III, moving to a discrete prior for treatment effects, and stating the hypothesis test may only depend upon Phase III data.

The approach taken in this chapter to model a programme is valuable in the sense that it allows us to model a programme without too many simplifying assumptions. In particular, we may specify a continuous prior for the treatment effects which is updated to make decisions within the Phase II/III programme in a Bayesian decision making framework with detailed optimal decision rules for each decision point. We believe the approach taken here would be of interest to stakeholders and decision makers in late phase drug development.

Chapter 3 Appendices

3.A Exploring the choice of n_2 in Decision 2

As discussed in the simulation study, both the optimal n_2 and corresponding expected gain in Decision 2 may be determined in certain situations by just the posterior mean of θ_{i*}.

In the below figure, we plot a typical decision curve encountered in Decision 2.

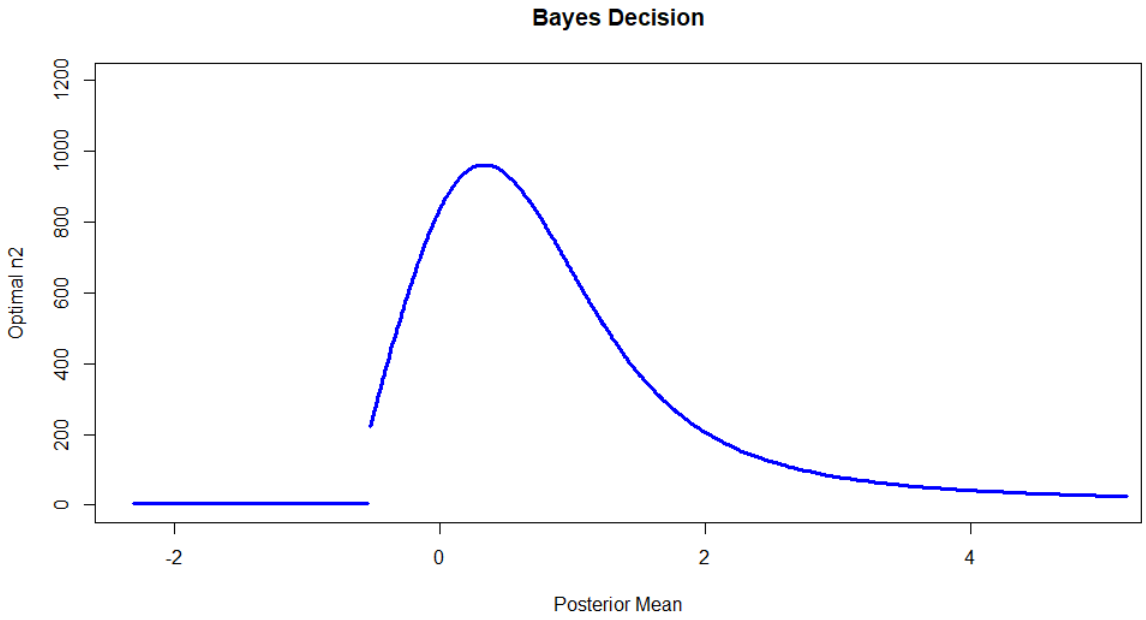

Figure 3-10: An optimal decision curve for Decision 2.

The decision rule plotted above has a few interesting features. Firstly, note that for low values of the posterior mean the optimal n_2 is 0. That is, if the Phase II data strongly suggest a negative treatment effect, then the best action to not perform a Phase III to save the cost of treating Phase III patients.

As the posterior mean increases, the optimal n_2 discontinuously jumps to a large positive value, and then continues to increase to a peak. As the posterior mean approaches 0, a non-insignificant amount of the posterior distribution is just above 0, where a large n_2 is needed to detect a difference in the hypothesis test.

As the posterior mean gets very large, the optimal choice of n_2 starts to decrease again as a smaller n_2 suffices to detect a difference in the hypothesis test.

We return to the discontinuity where the optimal choice of n_2 jumps from 1 to a large positive number as the posterior mean crosses a threshold. Figure 3-11 illustrates the mechanism behind this discontinuity. When the posterior mean is around the value the jump occurs, a small proportion of the posterior density will be small but positive. In order to detect this difference, the sample size must be substantial. There exists a decision between not performing the trial and performing a trial with a substantial sample size, and as the posterior mean increases, this leads to the discontinuous jump in the optimal sample size for Phase III.

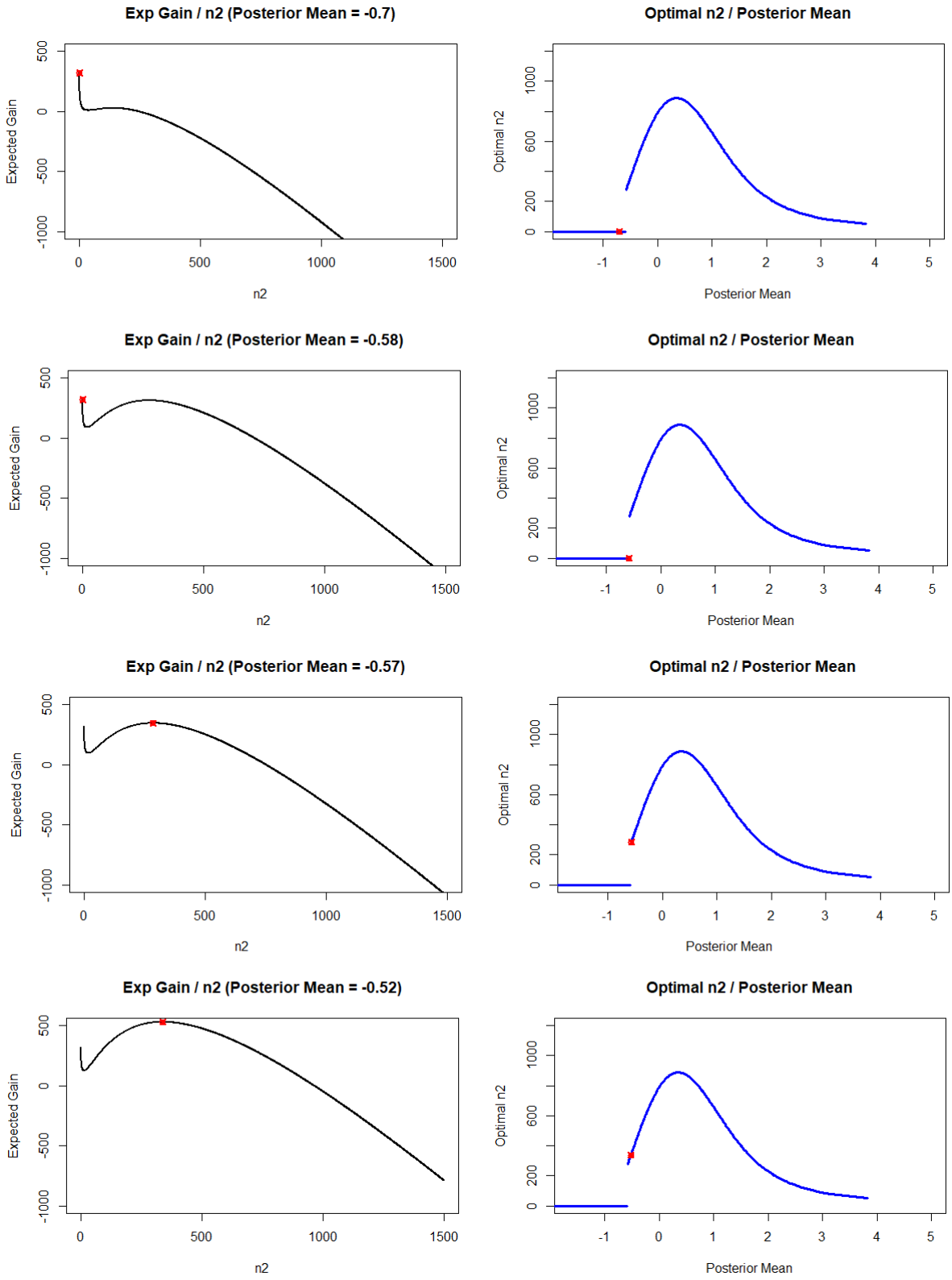

Figure 3-11: 4 pairs of figures for 4 increasing values of the posterior mean, showing how the discontinuity arrives in Figure 3-10. Each figure on the left shows the expected gain for different values of n_2, with the maximising value of n_2 indicated by a red cross on the right figure of the optimal decision curve as a function of the posterior mean of θ_{i*}.

3.B Properties of *Special Prior 1*

In Section 3.6.1, we defined *Special Prior 1*. We show properties of this prior in this section.

Let Σ_0 be

$$[\Sigma_0]_{i,j} = \begin{cases} c & \text{if } i = j \\ c\ (1+\sqrt{K})^{-1} & \text{if } i \neq j \end{cases}, \tag{3.29}$$

for some constant c.

We show that for any i in $\{1, ..., K\}$, the posterior distribution for the treatment effect of treatment i depends only on the maximum likelihood estimate for its treatment effect from Phase II data. In particular it does not depend any of the non-ith elements of the vector $\hat{\boldsymbol{\theta}}_1$.

From Equation 3.14, we have $\hat{\boldsymbol{\theta}}_1|\boldsymbol{\theta} \sim N(\boldsymbol{\theta}, \Sigma)$. We note that

$$\Sigma = \frac{\sigma^2(1+K^{-1/2})}{cn_1^{(t)}}\Sigma_0. \tag{3.30}$$

Let $\sigma'^2 := \frac{\sigma^2(1+K^{-1/2})}{cn_1^{(t)}}$, such that $\Sigma = \sigma'^2\Sigma_0$. We consider the posterior distribution of $\boldsymbol{\theta}$ given $\hat{\boldsymbol{\theta}}_1$. By standard theory, this is multivariate normal with mean

$$\begin{aligned}(\Sigma_0^{-1} + \Sigma^{-1})^{-1}(\Sigma^{-1}\hat{\boldsymbol{\theta}}_1 + \Sigma_0^{-1}\boldsymbol{\theta}_0) &= ((1+\sigma'^{-2})\Sigma_0^{-1})^{-1}(\sigma'^{-2}\Sigma_0^{-1}\hat{\boldsymbol{\theta}}_1 + \Sigma_0^{-1}\boldsymbol{\theta}_0) \\ &= (1+\sigma'^{-2})^{-1}(\sigma'^{-2}\hat{\boldsymbol{\theta}}_1 + \boldsymbol{\theta}_0).\end{aligned} \tag{3.31}$$

In particular the posterior distribution mean for the treatment effect of treatment i^* satisfies

$$\breve{\theta}_{i^*,1} = (1+\sigma'^{-2})^{-1}(\sigma'^{-2}\hat{\theta}_{i^*,1} + \theta_{i^*,0}), \tag{3.32}$$

which only depends upon the i^*th elements of $\hat{\boldsymbol{\theta}}_1$ and $\boldsymbol{\theta}_0$.

If i^* is index of maximum element of $\hat{\boldsymbol{\theta}}_1$, the Dunnett multiplicity adjusted p-value $\tilde{p}_{i^*,1}$ depends only on the ith element of $\hat{\boldsymbol{\theta}}_1$. Therefore there exists a bijection between $\breve{\theta}_{i^*,1}$ and $\tilde{p}_{i^*,1}$ in this case.

3.C Group sequential computations

3.C.1 Calculating the probability of rejection for a distributed θ

In Jennison and Turnbull (2000), the notation ψ_k is used to represent the probability of rejection at stage k. The authors treat the treatment effect θ as fixed. However, in many applications studied in this chapter, the probabilities relating to a group sequential design need to be evaluated over a distribution of possible treatment effects. That is, probabilities such as ψ_k need to be evaluated over a distribution $\pi(\theta)$ on θ, which is typically Gaussian. The first approach one may take to computing the probability of rejection ψ_k when θ is distributed according to $\pi(\theta)$, denoted by $\psi_{\pi,k}$, is to simply integrate the probability over a range of possible θ values, weighting by the the corresponding distribution $\pi(\theta)$ as such:

$$\begin{aligned}\psi_{\pi,k} &:= \int_{\mathbb{R}} \psi_k(\theta)\pi(\theta)d\theta \\ &= \int_{\mathbb{R}} \int_{a_1}^{b_1} ... \int_{a_{k-1}}^{b_{k-1}} \int_{b_k}^{\infty} f_1(s_1;\theta) f_2(s_1,s_2;\theta)...f_k(s_{k-1},s_k,\theta)\ ds_k...ds_1\ \pi(\theta)\ d\theta\end{aligned} \tag{3.33}$$

for densities f_1,f_2,...,f_S as in Jennison and Turnbull (2000) but on the score statistic scale, and stopping boundaries $a_1, a_2, ..., a_S$,$b_1, b_2..., b_S$ also on the score statistic scale.

The authors show that ψ_k can be re-written in terms of iteratively defined sub-densities. Thus we may rewrite $\psi_{\pi,k}$ as

$$\psi_{\pi,k} = \int_{a_{k-1}}^{b_{k-1}} \int_{\mathbb{R}} g_{k-1}(s_{k-1};\theta) e_{k-1}(s_{k-1},b_k;\theta)\pi(\theta)\ d\theta\ ds_{k-1}, \tag{3.34}$$

where $g_1, ..., g_k$ are the sub-densities on the score statistic scale and are defined iteratively by

$$\begin{aligned} g_1(s_1;\theta) &= f_1(s_1;\theta) \\ g_k(s_k;\theta) &= \int_{a_{k-1}}^{b_{k-1}} g_{k-1}(s_{k-1};\theta) f_k(s_{k-1},s_k;\theta)\ ds_{k-1}. \end{aligned} \tag{3.35}$$

The advantage in using this formulation is that approximations of the sub-densities can be computed iteratively. However in the above form, integrating over the distribution $\pi(\theta)$ on the outside of the integral is computationally expensive. The approach we take here is to move this integral within the other to become the innermost integral and is motivated by Barber and Jennison (2002). We write

$$\psi^*_{\pi,k} := \int_{a_{k-1}}^{b_{k-1}} g^*_{k-1}(s_{k-1}) e^*_{k-1}(s_{k-1},b_k)\ ds_{k-1}, \tag{3.36}$$

$$\begin{aligned} \text{where } g^*_1(s_1) &:= \int_{\mathbb{R}} f_1(s_1;\theta)\ \pi(\theta)\ d\theta, \\ g^*_k(s_k) &:= \int_{a_{k-1}}^{b_{k-1}} g^*_{k-1}(s_{k-1}) \int_{\mathbb{R}} f_k(s_{k-1},s_k;\theta)\pi_{\theta|S_{k-1}=s_{k-1}}(\theta)\ d\theta\ ds_{k-1}, \text{ and} \\ e^*_{k-1}(s_{k-1},b_k) &:= \int_{\mathbb{R}} e_{k-1}(s_{k-1},b_k;\theta)\pi_{\theta|S_{k-1}=s_{k-1}}(\theta)\ d\theta \end{aligned}$$

We prove that using the computationally faster $\psi^*_{\pi,k}$ is equivalent to using $\psi_{\pi,k}$.

$\psi_{\pi,k} = \psi^*_{\pi,k}$ for any distribution π and $k = 1, ..., K$.

Proof. By comparing the forms of $\psi^*_{\pi,k}$ and $\psi_{\pi,k}$, it is sufficient to prove that for any k, θ, and s_{k-1},

$$g^*_{k-1}(s_{k-1})\pi_{\theta|S_{k-1}=s_{k-1}}(\theta) = g_{k-1}(s_{k-1},\theta)\pi(\theta). \tag{3.37}$$

Firstly, we note that we can re-write $g_k(s_k;\theta)$ and $g^*_k(s_k;\theta)$ in the following ways:

$$
\begin{aligned}
g_k(s_k;\theta) &= \int_{a_{k-1}}^{b_{k-1}} g_{k-1}(s_{k-1};\theta) f_k(s_{k-1},s_k;\theta)\ ds_{k-1} \\
&= \int_{a_{k-1}}^{b_{k-1}} \int_{a_{k-2}}^{b_{k-2}} g_{k-2}(s_{k-2};\theta) f_{k-1}(s_{k-2},s_{k-1};\theta)\ ds_{k-2} f_k(s_{k-1},s_k;\theta)\ ds_{k-1} \\
&= \int_{a_{k-1}}^{b_{k-1}} \int_{a_{k-2}}^{b_{k-2}} ... \int_{a_1}^{b_1} f_1(s_1;\theta) f_2(s_1,s_2;\theta) ... f_k(s_{k-1},s_k;\theta)\ ds_1 ... ds_{k-1},
\end{aligned}
$$

and

$$
\begin{aligned}
g_k^*(s_k) &= \int_{a_{k-1}}^{b_{k-1}} g_{k-1}^*(s_{k-1}) \int_{\mathbb{R}} f_k(s_{k-1},s_k;\theta) \pi_{\theta|S_{k-1}=s_{k-1}}(\theta)\ d\theta\ ds_{k-1} \\
&= \int_{a_{k-1}}^{b_{k-1}} \int_{a_{k-2}}^{b_{k-2}} g_{k-2}^*(s_{k-2}) \int_{\mathbb{R}} f_{k-1}(s_{k-2},s_{k-1};\theta) \pi_{\theta|S_{k-2}=s_{k-2}}(\theta)\ d\theta\ ds_{k-2} \\
&\quad \times \int_{\mathbb{R}} f_k(s_{k-1},s_k,\theta) \pi_{\theta|S_{k-1}=s_{k-1}}(\theta)\ d\theta\ ds_{k-1} \\
&= \int_{a_{k-1}}^{b_{k-1}} \int_{a_{k-2}}^{b_{k-2}} g_{k-2}^*(s_{k-2}) \int_{\mathbb{R}} f_{k-1}(s_{k-2},s_{k-1};\theta) \pi_{\theta|S_{k-2}=s_{k-2}}(\theta)\ d\theta \\
&\quad \times \int_{\mathbb{R}} f_k(s_{k-1},s_k,\theta) \pi_{\theta|S_{k-1}=s_{k-1}}(\theta)\ d\theta\ ds_{k-2}\ ds_{k-1} \\
&= ... \\
&= \int_{a_{k-1}}^{b_{k-1}} ... \int_{a_1}^{b_1} \int_{\mathbb{R}} f_1(s_1;\theta) \pi_\theta(\theta)\ d\theta \int_{\mathbb{R}} f_2(s_1,s_2,\theta) \pi_{\theta|S_1=s_1}(\theta)\ d\theta \\
&\quad \times ... \times \int_{\mathbb{R}} f_k(s_{k-1},s_k,\theta) \pi_{\theta|S_{k-1}=s_{k-1}}(\theta)\ d\theta\ ds_1 ... ds_{k-1}.
\end{aligned}
$$

Now, Bayes' Theorem implies the following relation;

$$
\pi_{\theta|S_{k-1}=s_{k-1}}(\theta) = \frac{g_{k-1}(s_{k-1};\theta)\pi(\theta)}{\int_{\mathbb{R}} g_{k-1}(s_{k-1};\theta)\pi(\theta)d\theta}. \tag{3.38}
$$

Consider the following:

Lemma
For any k and s_k,

$$
g_k^*(s_k) = \int g_k(s_k;\theta)\pi(\theta)d\theta. \tag{3.39}
$$

Assume the Lemma holds. Then we use equations 3.38 and 3.39 to show Equation 3.37 holds:

$$
\begin{aligned}
g_{k-1}^*(s_{k-1})\pi_{\theta|S_{k-1}}(\theta) &= \int g_{k-1}(s_{k-1},\theta)\pi(\theta)d\theta \frac{g_{k-1}(s_{k-1},\theta)\pi(\theta)}{\int g_{k-1}(s_{k-1},\theta)\pi(\theta)d\theta} \\
&= g_{k-1}(s_{k-1},\theta)\pi(\theta)
\end{aligned} \tag{3.40}
$$

This is sufficient to complete the proof. We finish by proving the Lemma.

Proof of Lemma:

Note that Bayes' Theorem implies

$$\begin{aligned}\pi_{\theta|S_1=s_1}(\theta) &= \frac{f_1(s_1;\theta)\pi(\theta)}{\int_{\mathbb{R}} f_1(s_1;\theta)\pi(\theta)d\theta}, \text{ and for } r = 2, ..., k-1, \\ \pi_{\theta|S_r=s_r}(\theta) &= \frac{\int_{a_{r-1}}^{b_{r-1}} ... \int_{a_1}^{b_1} f_1(s_1;\theta)f_2(s_1,s_2;\theta)...f_r(s_{r-1},s_r;\theta)\pi(\theta)ds_1...ds_{r-1}}{\int_{\mathbb{R}}\int_{a_{r-1}}^{b_{r-1}} ... \int_{a_1}^{b_1} f_1(s_1;\theta)f_2(s_1,s_2;\theta)...f_r(s_{r-1},s_r;\theta)\pi(\theta)ds_1...ds_{r-1}d\theta}.\end{aligned} \tag{3.41}$$

Therefore one may write

$$\begin{aligned}g_k^*(s_k) = &\int_{a_{k-1}}^{b_{k-1}} ... \int_{a_1}^{b_1} \\ &\times \int_{\mathbb{R}} f_1(s_1;\theta)\pi(\theta)d\theta \\ &\times \int_{\mathbb{R}} f_2(s_1,s_2;\theta)\frac{f_1(s_1;\theta)\pi(\theta)}{\int_{\mathbb{R}} f_1(s_1;\theta)\pi(\theta)d\theta}d\theta \\ &\times \int_{\mathbb{R}} f_3(s_2,s_3;\theta)\frac{\int_{a_1}^{b_1} f_1(s_1;\theta)f_2(s_1,s_2;\theta)\pi(\theta)ds_1}{\int_{\mathbb{R}}\int_{a_1}^{b_1} f_1(s_1;\theta)f_2(s_1,s_2;\theta)\pi(\theta)ds_1d\theta}d\theta \\ &\times ... \\ &\times \int_{\mathbb{R}} f_k(s_{k-1},s_k;\theta)\frac{\int_{a_{k-2}}^{b_{k-2}} ... \int_{a_1}^{b_1} f_1(s_1;\theta)...f_{k-1}(s_{k-2},s_{k-1};\theta)\pi(\theta)ds_1...ds_{k-2}}{\int_{\mathbb{R}}\int_{a_{k-2}}^{b_{k-2}} ... \int_{a_1}^{b_1} f_1(s_1;\theta)...f_{k-1}(s_{k-2},s_{k-1};\theta)\pi(\theta)ds_1...ds_{k-2}d\theta}d\theta \\ &ds_1...ds_{k-1} \\ = &\int_{a_{k-1}}^{b_{k-1}} ... \int_{a_1}^{b_1}\int_{\mathbb{R}} f_1(s_1;\theta)f_2(s_1,s_2;\theta)...f_k(s_{k-1},s_k;\theta)\pi(\theta)d\theta ds_1...ds_{k-1} \\ = &\int_{\mathbb{R}}\int_{a_{k-1}}^{b_{k-1}} ... \int_{a_1}^{b_1} f_1(s_1;\theta)f_2(s_1,s_2;\theta)...f_k(s_{k-1},s_k;\theta)\pi(\theta)ds_1...ds_{k-1}d\theta \\ = &\int g_k(s_k;\theta)\pi(\theta),\end{aligned}$$

which completes the proof. □

Similarly, one may show for the probabilities of acceptance at stage k, $\phi_{\pi,k} = \phi^*_{\pi,k}$, where

$$\phi_{\pi,k} = \int_{a_{k-1}}^{b_{k-1}} \int_{\mathbb{R}} g_{k-1}(s_{k-1};\theta)\ e'_{k-1}(s_{k-1},a_k;\theta)\ \pi(\theta)\ ds_{k-1}\ d\theta, \tag{3.42}$$

for probability of acceptance at stage k, $e'_{k-1}(s_{k-1},a_k;\theta)$, which may be derived in a similar way to its probability of rejection counterpart, $e_{k-1}(s_{k-1},b_k;\theta)$, and

$$\phi^*_{\pi,k} := \int_{a_{k-1}}^{b_{k-1}} g^*_{k-1}(s_{k-1})\ e'^*_k(s_{k-1},a_k)\ ds_{k-1}, \tag{3.43}$$

where

$$e'^*_k(s_{k-1},a_k) := \int_{\mathbb{R}} e'_{k-1}(s_{k-1},a_k;\theta)\ \pi_{\theta|S_{k-1}=s_{k-1}}(\theta)\ d\theta$$

Following this proposition, the probability of rejection in a group sequential design with K stages when θ is distributed according to $\pi(\theta)$ may be written as

$$p_\pi(\text{ cross rejection boundary }) = \sum_{k=1}^{K} \psi_{\pi,k} = \sum_{k=1}^{K} \psi^*_{\pi,k} \tag{3.44}$$

Using the $\psi^*_{\pi,k}$ form allows computations to be performed much faster when θ has some distribution.

Given $\psi_{\pi,k}$ and $\psi^*_{\pi,k}$ have been calculated for all k, properties about the sample size of the group sequential design can be easily deduced.

3.C.2 Calculating the expected gain when θ is random, ζ depends upon θ

This method may be extended the calculate the expected gain of a treatment with treatment effect θ, which has some distribution, entering a group sequential design when the gain function depends upon θ.

In this method, one calculates expected gain in addition to the probability of rejection for a normally distributed θ. This involves integrating above the rejection boundaries $\boldsymbol{b}$ at each stage to calculate the expected gain at the previous stage. Denote $\mathfrak{e}_k(\theta)$ as the expected gain from the GSD with treatment effect θ from stopping at stage k, and $\mathcal{G}(\theta, s_k)$ the gain form stopping at stage k at s_k when theta is θ.

In this case, the quantity

$$\begin{aligned} \mathfrak{e}_{\pi,k} &:= \int_{\mathbb{R}} \psi_k(\theta)\pi(\theta)d\theta \\ &= \int_{\mathbb{R}} \int_{a_1}^{b_1} ... \int_{a_{k-1}}^{b_{k-1}} \int_{b_k}^{\infty} f_1(s_1;\theta)...f_s(s_{k-1}, s_k, \theta)\ \mathcal{G}(\theta, s_k)\ d_{s_k}...ds_1\ \pi(\theta)\ d\theta \end{aligned} \tag{3.45}$$

may be written as

$$\mathfrak{e}^*_{\pi,k} = \int_{a_{k-1}}^{b_{k-1}} g^*_k(s_{k-1}) \int_{\mathbb{R}} \int_{b_k}^{\infty} \mathcal{G}(\theta, s_k)\ f_k(s_{k-1}, s_k;\theta)\ ds_k\ \pi_{\theta|S_{k-1}=s_{k-1}}(\theta)\ d\theta\ ds_{k-1}. \tag{3.46}$$

The proof that $\mathfrak{e}_{\pi,k} = \mathfrak{e}^*_{\pi,k}$ is similar to the previous case in Appendix 3.C. The overall expected gain of the GSD may then be written as

$$\mathfrak{e}_\pi = \sum_{k=1}^{S} \mathfrak{e}^*_{\pi,k}. \tag{3.47}$$

4 The Value of Dose Response Modelling in Phase II/III Programmes

4.1 Dose response modelling

4.1.1 An introduction

In Chapter 3, we treated each treatment as distinct and made no assumptions about how the mean responses for efficacy for different treatments were related. However in many Phase II/III programmes, a key part of the development process is the identification of the correct dose of a treatment when there is some relationship between the mean responses for efficacy at different dose levels. In this chapter, we examine the problem of a Phase II/III programme with dose selection, where the treatments entering Phase II are assumed to be doses of the same treatment. Using a similar framework to Chapter 3, we assess the value that different dose response modelling approaches may bring to the programme.

Phase I clinical trials are concerned with finding a maximum tolerated dose. That is, the highest dose of treatment that does not have unacceptable risk of adverse events. Phase III involves confirmatory trials to provide evidence of efficacy and an acceptable risk of adverse events of a single treatment. Phase II is therefore often concerned with dose ranging studies. The purpose of a dose ranging study is to identify whether a Phase III study should be performed, and the dose to take forward to Phase III. Sometimes, the number of patients that should be used in Phase III will also be influenced by results from the dose ranging study.

A drug or treatment is intended to have beneficial effects to patients, but it will also have unwanted effects. These unwanted effects may be called adverse events. As the dose increases, both the beneficial effects and risk of adverse events may increase together. Dose finding is the problem of finding a dose with the right balance of beneficial effects and risk of an advance event. The ICH E4 document on 'Dose Response Information to Support Drug Registration' ICH (1998) contains the primary regulatory guidance.

4.1.2 Modelling dose and efficacy

A common approach is to model the relationship between dose and efficacy with parametric dose response models. Safety is not always modelled in the same way, due to the potential difficulties of obtaining accurate quantitative measurements. In many cases, it is assumed

that the efficacy plateaus as the dose increases beyond a certain level, whilst the risk of adverse effects increase monotonically.

The dose finding problem often becomes that of trying to find the smallest dose that provides almost maximal efficacy. Safety aspects of each dose may then be modelled quantitatively using information learned from previous trials in the therapeutic area, Phase I studies, and perhaps even Phase II studies when the safety responses are available in a short period of time. The trade-off between wanted and unwanted effects may be analysed using decision theory or clinical utility indices.

In order to get information about the relationship between dose and efficacy, one needs to place the doses at appropriate intervals. In practice, information about the dose response relationship is limited when designing the study, so one solution is to use more doses covering a wide range in order to attempt to capture the true dose response curve. Phase I trials will provide information about the maximum tolerated dose which may be an upper bound on any doses studied. Basic rules of thumb in industry advise the use of 4-7 doses with a range such that the largest dose is ten times larger than the lowest dose. The doses may be spaced out uniformly on the log dose scale.

4.1.3 Dose response models

Let $\mu(d, \boldsymbol{\theta})$ represent the mean patient efficacy response at dose d for some parameter vector $\boldsymbol{\theta}$.

A popular dose response model is the 3-parameter $E_{\max}$ model. For this model, $\mu(d, \boldsymbol{\theta})$ takes the form

$$\mu(d, \boldsymbol{\theta}) = \alpha_1 + \alpha_2 \frac{d}{\beta + d}, \tag{4.1}$$

where $\boldsymbol{\theta} = (\boldsymbol{\alpha}, \beta)$ are the model parameters with $\boldsymbol{\alpha} = (\alpha_1, \alpha_2)$. Parameter α_1 represents the response at $d = 0$, α_2 represents the increase from α_1 to the maximum response as the dose gets large, and β (ED50) the dose such that the response is $\alpha_1 + \frac{1}{2}(\alpha_2 - \alpha_1)$.

A commonly used more general model is the 4-parameter $E_{\max}$ model where $\mu(d, \boldsymbol{\theta})$ takes the form

$$\mu(d, \boldsymbol{\theta}) = \alpha_1 + \alpha_2 \frac{d^h}{\beta^h + d^h}, \tag{4.2}$$

where the Hill parameter $h > 0$ controls the steepness of the curve and is included in the definition of $\boldsymbol{\theta}$.

The $E_{\max}$ dose response model may be derived from pharmacological principles: see Bretz and Xun (2017). The appropriateness of the Emax model for modelling dose and efficacy response data has been evaluated by Thomas et al. (2014). In this paper, a large number of efficacy dose response relationships for small molecules were evaluated and it was concluded that in almost all situations the $E_{\max}$ curve described the data adequately well.

Given that the true underlying dose response relationship takes the form of an $E_{\max}$ model, there are other functions that can adequately describe the data over a particular subset of the dose range. An exponential or linear function can be used to obtain local approximations

of the true underling $E_{\max}$ model. Because of this, extrapolation beyond a specified dose range upon which a model is fitted must be done with care.

Dose response relationships that are not monotonic increasing may occur due to pharmacological reasons. Lagarde et al. (2015) detail cases dose response relationships where receptor desensitisation and negative feedback mechanisms lead to a decrease in efficacy for high doses. The quadratic and beta dose response functions can accommodate non-monotonic dose response relationships.

In addition to the $E_{\max}$ function, the Table 4.1 lists 6 further dose response functions. We denote $B(\delta_1, \delta_2)$ as the Beta function.

Table 4.1: Dose response functions from Bretz et al. (2005)

Name	**Dose Response Function**	**Parameter Constraints**
Exponential	$E_0 + E_1(\exp(d/\delta) - 1)$	$\delta > 0$
Power	$E_0 + E_1 d^{\delta}$	$\delta > 0$
Linear	$E_0 + \delta d$	
Linear Log	$E_0 + E_1 \log(d + c)$	$c > 0$
Quadratic	$E_0 + \beta_1 d + \beta_2 d^2$	
Beta	$E_0 + E_{\max} B(\delta_1, \delta_2)(d/D)^{\delta_1}(1 - d/D)^{\delta_2}$	$\delta_1, \delta_2, D > 0$

The Use of Bayesian Methods

Inference using dose response models can be performed in a frequentist setting where estimates for the parameters of the dose response model are obtained given observed data, with some measure of uncertainty. These estimates may be obtained using methods such as maximum likelihood estimation.

Alternatively, one may use a Bayesian approach where priors are attached to the parameters of the dose response model and the posterior distribution of these parameters are derived given the observed data. Methods for finding these posterior distributions may include Markov Chain Monte Carlo (MCMC) or other sampling approaches. In Appendix 4.A, we outline a rejection sampling algorithm that may be used to sample from the posterior distribution of the parameters of any dose response model in Table 4.1. This method is far more efficient than the MCMC approach.

In this chapter, we shall take the Bayesian approach.

4.1.4 MCP-Mod

Bretz et al. (2005) first describe the procedure MCP-Mod, which amalgamates multiple comparison procedures and model-based approaches to tackle the dose finding problem. The method starts with a set of potential models for the dose response relationship. Given the data, the procedure conducts a contrast test for each dose response model in order to identify if there is a dose response relationship, whilst controlling the FWER of the contrast tests using multiple comparison procedures (MCP step). If any of the models are appropriate, it selects the 'best' model. Inference may be performed using this model (Mod step); for example, to estimate a target dose of interest.

MCP-Mod has attracted attention since its inception, with R packages and SAS procedures written for it. König (2015) extends the method by allowing pairwise dose control comparisons in a closed testing procedure, and allowing combination tests to perform interim analyses to change the models under consideration, sample sizes, and doses. Commercial software such as EAST (EAST-6 (2019)) have implemented MCP-Mod procedures as of 2019. Trials such as Worm et al. (2017) have used MCP-Mod methodology.

The original MCP-Mod approach was for a single, normally distributed endpoint in a parallel-group design. We outline the approach in Appendix 4.B.

Use of MCP-Mod Within a Phase II/III Programme

MCP-Mod is a procedure suitable for the problem when there is uncertainty as to the true relationship between dose and the mean efficacy responses. By specifying a set of candidate of models, the procedure may identify which, if any, are best suited to the observed data. In this chapter, we assess the value of using this approach in comparison to simpler dose response models.

Extensions

The MCP-Mod procedure has received much attention since this initial formulation in Bornkamp (2006). The method has been extended to general linear models and can be used with combination tests. In Appendix 4.D, we outline these extensions and suggest other generalisations to avoid the use of *guesstimates* and improve the power of the multiple contrast test.

4.1.5 Our Phase II/III programme framework

In Chapter 3, we specified a Phase II/III programme framework to assess the benefit of using adaptive designs within the programme when the treatments were not assumed to have a relationship between dose and efficacy. Here, we specify a Phase II/III programme framework to assess the benefit of using dose response models when the doses and efficacy responses have some relationship. Phase III is fixed sample with no use of Phase II data in the final hypothesis test. As in Chapter 3, we find the optimal decision rules according to Bayesian decision theory in order to optimise the programme.

Define $y_{i,j}$ as the observed response for patient j at dose d_i for for $i = 1, ..., K$, and $j = 1, ..., n_i$, with $i = 1$ corresponding to the control arm. We suppose the doses are such that $d_1 < d_2 < ... < d_K$. Consider the model

$$y_{i,j} = \mu(d_i) + \epsilon_{i,j}, \quad \epsilon_{i,j} \overset{\text{iid}}{\sim} N(0, \sigma^2), \tag{4.3}$$

Thus, the observed response for patient j at dose d_i is normally distributed with a known homogeneous variance across all doses, and the mean response for a particular dose d_i is given by $\mu(d_i)$. We suppose the dose response model with parameters $\boldsymbol{\theta}$ specifies $\mu(d_i) = f(d_i, \boldsymbol{\theta})$. Denote by $\boldsymbol{\mu}$ the vector of mean responses $(\mu(d_1), ..., \mu(d_K))^T$.

The Phase II/III programme framework is similar to the one in Chapter 3, which chooses the Phase II sample size n_1 (Decision 1), performs Phase II, and then chooses the dose to take forward i^* and Phase III sample size n_2, both based on the Phase II data (Decision 2).

- **Decision 1**: Choose n_1 using the prior distribution on the treatment effect vector $\boldsymbol{\theta}$ according to the programme assumptions.
- Observe Phase II responses with n_1 patients on each of the K doses, and make statistical inferences about the treatment effect vector $\boldsymbol{\theta}$ according to the programme assumptions.
- **Decision 2**: Choose n_2 and i^* based on the posterior distribution of $\boldsymbol{\theta}$ given the Phase II data.
- Observe Phase III responses of dose i^* and placebo with n_2 patients on each arm and perform a statistical hypothesis test using only Phase III responses.

The key difference here to the approach in Chapter 3 is that the dose response model used will affect both the dose i^* that is taken forward and the Phase III sample size n_2 in Decision 2. Information from other doses affects the estimate of $\mu(d_i)$.

Similarly to Chapter 3, we find the optimal decisions in Decision 1 and 2 according to Bayesian decision theory. The gain function is used to calculate these optimal decision rules, but in contrast to Chapter 3, must be influenced by the increased risk of adverse events for higher doses.

We incorporate the risks of adverse events at each dose with a multiplicative penalty for each successive dose $\boldsymbol{S} = (s_2, ..., s_K)$. For dose i, s_i will represent the probability the risk of adverse events is at a satisfactory level which will not stop the revenue being realised. This represents the risk that a safety problem is not found post-marketing. As the dose increases, this probability decreases such that $s_2 \geq s_3 \geq ... \geq s_K$. We denote the indicator function that a safety problem occurs as $\mathbb{1}_{(\text{No safety problems for drug } i)}$ with the expected value s_i.

Using notation from Chapter 3, the gain function is specified in the following way:

$$\mathcal{G}(\mathcal{I}_2, \theta_{i^*}) := G\ \mathbb{1}_{\{H_{i^*} \text{ is rejected}\}} \mathbb{1}_{(\text{No safety problems for drug } i^*)} - K\gamma_1 n_1 - 2\gamma_2 n_2. \tag{4.4}$$

One may compare the values of optimised programmes when components of the programme are changed.

4.2 Quantifying the value of dose response modelling in a Phase II/III programme

4.2.1 Introduction

In Chapter 3, we assessed the value of introducing adaptive methods in a Phase II/III programme by specifying different programmes within a general framework and optimising each one by finding the optimal decision rules at each decision point according to Bayesian decision theory. This section aims to assess the value of introducing dose response modelling methods in a Phase II/III programme. Similarly to before, we must specify different programmes within a general framework and find the optimal decision rules at each decision point.

4.2.2 Case Study 1: The value of using an Emax model in a Phase II/III programme

Case study setup

Suppose the mean efficacy responses $\boldsymbol{\mu}$ on doses $d_1, ..., d_K$ are from the 3-parameter Emax model. That is,

$$\boldsymbol{\mu} = (\mu(d_1, \boldsymbol{\theta}), ..., \mu(d_K, \boldsymbol{\theta})) \tag{4.5}$$

where $\mu(d, \boldsymbol{\theta})$ is defined in Equation 4.1.

Let $N^+(\cdot, \cdot)$ be the positively truncated normal distribution with mean μ_β, and variance Λ_β such that a sample may be obtained from this distribution by repeatedly sampling from $N(\mu_\beta, \Lambda_\beta)$ until the sample is positive.

We specify the prior distribution of the Emax model parameters $\boldsymbol{\theta} = \{\boldsymbol{\alpha}, \beta\}$. In particular, we specify the priors

$$\boldsymbol{\alpha} \sim N(\boldsymbol{\mu_\alpha}, \Lambda_{\boldsymbol{\alpha}}), \text{ and } \beta \sim N^+(\mu_\beta, \Lambda_\beta). \tag{4.6}$$

Below, we define three programmes which we shall compare. The differences between the programmes lie in the choice of model of the mean efficacy responses $\boldsymbol{\mu}$ and the priors attached to parameters within the model. The posterior distribution of $\boldsymbol{\mu}$ given the Phase II data depends upon these choices.

Programme 1 assumes no distinct relationship between the mean efficacy responses for different doses. The model for Programme 1 specifies the mean efficacy response $\boldsymbol{\mu}$ follows a multivariate normal distribution with a diagonal covariance matrix. Programme 2 allows dependence between the elements of $\boldsymbol{\mu}$ within the model by allowing the covariance matrix to be non-diagonal. Programme 3 uses the correct $E_{\max}$ model.

The vector of mean responses at each dose is defined as $\boldsymbol{y}$ and follows the distribution

$$\boldsymbol{y} \sim N(\boldsymbol{\mu}, \text{diag}(\sigma^2/n_1, ..., \sigma^2/n_K)). \tag{4.7}$$

Programme 1 (MVN prior for $\boldsymbol{\mu}$ with diagonal covariance matrix)

- Specify a MVN prior $\boldsymbol{\mu} \sim N(\boldsymbol{\mu}_0, \Sigma_0)$, where Σ_0 is diagonal.
- Given Phase II data $\boldsymbol{y}$, use posterior distribution $\boldsymbol{\mu}|\boldsymbol{y}$ to make decisions in Decision 2.

Programme 2 (MVN prior for $\boldsymbol{\mu}$ with non-diagonal covariance matrix)

- Specify a MVN prior on the responses $\boldsymbol{\mu} \sim N(\boldsymbol{\mu}_0, \Sigma_0)$, where Σ_0 is not necessarily diagonal.
- Given Phase II data $\boldsymbol{y}$, use posterior distribution $\boldsymbol{\mu}|\boldsymbol{y}$ to make decisions in Decision 2.

Programme 3 (Emax model for $\boldsymbol{\mu}$)

- $\boldsymbol{\mu} = (\mu(d_1, \boldsymbol{\theta}), ..., \mu(d_K, \boldsymbol{\theta}))$ as in Equation 4.5.
- Specify a prior for each of the Emax model parameters $\boldsymbol{\alpha} \sim N(\boldsymbol{\mu}_\alpha, \Lambda_\alpha)$ and $\beta \sim N(\mu_\beta, \Lambda_\beta)$
- Given Phase II data $\boldsymbol{y}$, use posterior distribution $\boldsymbol{\mu}|\boldsymbol{y}$, found from the posterior distributions $\boldsymbol{\alpha}|\boldsymbol{y}$ and $\beta|\boldsymbol{y}$, to make decisions in Decision 2.

The parameters of the prior distribution used for each programme are chosen to match the true prior distribution of efficacy responses as closely as possible. For Programmes 1 and 2, $\boldsymbol{\mu}_0$ and Σ_0 are chosen by finding the maximum likelihood estimates of these parameters given a large number of simulations of mean efficacy responses $\boldsymbol{\mu}$ generated from the Emax model with the true priors on the Emax model parameters as specified in Equation 4.6. For Programme 3, we use the true priors for $\boldsymbol{\alpha}$ and β specified in Equation 4.6.

Case study parameters

General parameters

We define the parameters of the simulation study. The 5 doses taken were at values $\boldsymbol{d} = (0, 0.05, 0.20.6, 1)$ with $K = 5$. Note that the first dose is the control arm. The standard deviation for responses was $\sigma = 3$ across all doses and patients.

Gain function parameters

$G = 35000$, $\gamma_1 = \gamma_2 = 1$, $\boldsymbol{S} = (0.9, 0.8, 0.75, 0.6)$.

Prior specification

We define two sets of priors for parameters of the Emax model, and the corresponding implied priors for $\boldsymbol{\mu}_0$ and Σ_0 in Programme 1 and 2. We say Case Study 1A and Case Study 1B for Case Study 1 with prior 1 and 2 respectively.

Prior 1 (Case Study 1A):

$$\mu_{\boldsymbol{\alpha}} = (0, 0.5)^T,\ \mu_\beta = 0,\ \Lambda_{\boldsymbol{\alpha}} = \begin{bmatrix} 0.5 & 0 \\ 0 & 0.5 \end{bmatrix}, \text{ and } \Lambda_\beta = 0.25.$$

Implied priors for $\boldsymbol{\mu}_0$ and Σ_0 in Programme 1:

$$\boldsymbol{\mu}_0 = (0.003, 0.152, 0.288, 0.391, 0.427) \text{ and}$$
$$\Sigma_0 = \begin{bmatrix} 0.500 & 0 & 0 & 0 & 0 \\ 0 & 0.578 & 0 & 0 & 0 \\ 0 & 0 & 0.694 & 0 & 0 \\ 0 & 0 & 0 & 0.818 & 0 \\ 0 & 0 & 0 & 0 & 0.870 \end{bmatrix}$$

Implied priors for $\boldsymbol{\mu}_0$ and Σ_0 in Programme 2:

$$\boldsymbol{\mu}_0 = (0.003, 0.152, 0.288, 0.391, 0.427) \text{ and}$$
$$\Sigma_0 = \begin{bmatrix} 0.500 & 0.500 & 0.501 & 0.501 & 0.501 \\ 0.501 & 0.578 & 0.616 & 0.636 & 0.642 \\ 0.501 & 0.616 & 0.694 & 0818 & 0.759 \\ 0.501 & 0.636 & 0.743 & 0.818 & 0.842 \\ 0.501 & 0.642 & 0.759 & 0.842 & 0.870 \end{bmatrix}$$

Prior 2 (Case Study 1B):

$$\mu_{\boldsymbol{\alpha}} = (0, 1)^T,\ \mu_\beta = 0.1,\ \Lambda_{\boldsymbol{\alpha}} = \begin{bmatrix} 0.5 & 0 \\ 0 & 1 \end{bmatrix}, \text{ and } \Lambda_\beta = 0.5$$

Implied priors for $\boldsymbol{\mu}_0$ and Σ_0 in Programme 1:

$$\boldsymbol{\mu}_0 = (0.000, 0.259, 0.525, 0.744, 0.823) \text{ and}$$

$$\Sigma_0 = \begin{bmatrix} 0.501 & 0 & 0 & 0 & 0 \\ 0 & 0.642 & 0 & 0 & 0 \\ 0 & 0 & 0.853 & 0 & 0 \\ 0 & 0 & 0 & 1.091 & 0 \\ 0 & 0 & 0 & 0 & 1.199 \end{bmatrix}$$

Implied priors for $\boldsymbol{\mu}_0$ and Σ_0 in Programme 2:

$$\boldsymbol{\mu}_0 = (0.000, 0.259, 0.525, 0.744, 0.823) \text{ and}$$

$$\Sigma_0 = \begin{bmatrix} 0.501 & 0.502 & 0.502 & 0.502 & 0.502 \\ 0.502 & 0.642 & 0.709 & 0.741 & 0.749 \\ 0.502 & 0.709 & 0.853 & 0.944 & 0.972 \\ 0.502 & 0.741 & 0.944 & 1.091 & 1.141 \\ 0.502 & 0.749 & 0.972 & 1.141 & 1.199 \end{bmatrix}$$

See Appendix 4.E for the implications of these prior distributions to the typical dose response curve.

Optimisation computations

Optimal decisions in Decision 2 are calculated over a discrete range of Phase III sample sizes N_2 using Monte Carlo simulation with 2000 realisations of the posterior distribution of the treatment effects $\boldsymbol{\theta}$ given the Phase II data. Optimal decisions in Decision 1 are calculated over Phase II sample sizes N_1 using Monte Carlo simulation with 1000 simulations of the true mean dose efficacy relationship $\boldsymbol{\mu}$.

In this simulation study, we allow the choices of Phase II sample sizes per arm to be $N_1 := \{0, 1, 10, 25, 50, ..., 125, 150, 200, 250, 300\}$ and correspondingly for Phase III $N_2 := \{0, 200, 400, ..., 1800, 2000\}$.

Results

We present the results of the simulation study in terms of the expected gain of each programme from Decision 1. We do this for each of the two priors considered.

Prior 1: Case Study 1A

Simulation Study Conclusions (Prior 1)

The results of the simulation study are shown in Figure 4-1, where the expected gain of Programme 1, 2, and 3 are plotted against different choices of n_1 in Decision 1. Of interest is the difference between the expected gain of different programmes.

Relative performance of all programmes (Prior 1)

Despite having a potential revenue of $G = 35,000$ units, the optimal programmes have expected gains of between 5000 and 13,000. This is due to a significant probability the treatments are no better (or even worse) than control, and due to the safety penalties applied to choosing the doses.

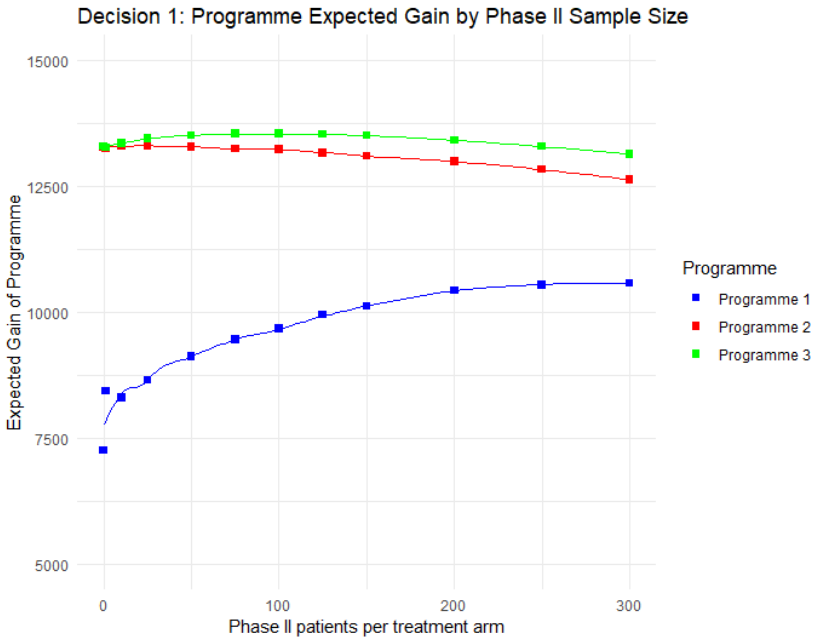

Figure 4-1: *Prior 1*: The expected gain over a range of different Phase II sample sizes. The standard error of each point estimate is less than 225. Due to the error sharing, the standard error between two estimates at the same n_1 but different programmes is approximately 150 for Programmes 1 and 2, 65 for Programmes 2 and 3.

For all values of Phase II sample size n_1, Programme 3 dominates Programme 2, which in turn dominates Programme 1. The difference in estimated expected gains as shown in Figure 4-1 is significant at each value for n_1 larger than 10. That is, for each value of n_1 larger than 10, the 95% confidence interval for the difference of the two expected gains of any two programmes does not contain 0.

Even though all the differences between all programmes are significant, the difference between Programme 1 and the others is particularly large. This provides evidence that in this scenario, the assumptions made in the model in Programme 1 may result in bad decisions being made for choices of i^*, n_2, severely harming the likelihood the programme has a large gain.

The difference between Programme 2 and 3 is much smaller. However on an absolute scale, a difference of several hundred units could still be argued to be important. As one unit represents the cost treating one patient, this is equivalent to saving several hundred times the cost of treating one patient, which is of the order of $20,000. Financially, this is a large amount.

Properties of Programme 1 at $n_1 = 0$ (Prior 1)

At $n_1 = 0$, no Phase II trial is performed and Phase III is designed based on the prior. For Programme 3, this is the correct prior (that is, the prior based on prior distributions on the Emax parameters which all data is simulated from). For Programmes 1 and 2 this is the multivariate normal prior approximated from the correct prior. Programmes 2 and 3 choose the same sample size of $n_2 = 1000$ patients, and the same dose of dose 4. Programme 1 also chooses dose 4 but with a lower sample size of $n_2 = 600$ patients, and has a lower expected gain because of this.

The reason for this may be found by looking at what the prior on $\boldsymbol{\mu}_0$ implies about the

treatment effect $\mu_k - \mu_1$ of treatment k,

$$\text{var}(\mu_k - \mu_1) = \text{var}(\mu_k) + \text{var}(\mu_1) - 2\text{cov}(\mu_1, \mu_k).$$

If, like in Programme 1, the covariance term is ignored, the prior stipulates the treatment effect of each dose is more variable than it is.

The shape of the expected gain of Programme 1 versus n_1 (Prior 1)

As a few patients are added to Programme 1, the expected gain decreases dramatically. As this programme uses the incorrect model to make inferences, there is a penalty not only for the cost of treating a patient, but by making non-optimal decisions based on using the data in a sub-optimal way. The optimal decision made when $n_1^{(t)} = 0$ is made according to the prior only, and in this case seems to be a fortuitously good choice. As patients are added, and decisions made on the posterior distribution of $\boldsymbol{\mu}$ given only a few patients, the decisions become more variable.

As n_1 increases further, the expected gain increases over the range of n_1 studied, but flattens off as as the number of patients reaches $n_1 = 300$ at a level less than Programmes 2 and 3.

The shapes of Programmes 2 and 3 (Prior 1)

Programmes 2 and 3 follow similar shapes with the expected gain increasing to a maximal n_1 value of approximately 30 and 125 respectively, before the cost of treating a patient dominates and the expected gain starts to decrease. Programme 2 uses the incorrect model so does not get the full benefit of additional patients when making decisions in Decision 2. This may be the reason for the maximal n_1 value being lower than in Programme 1.

Prior 2: Case Study 1B

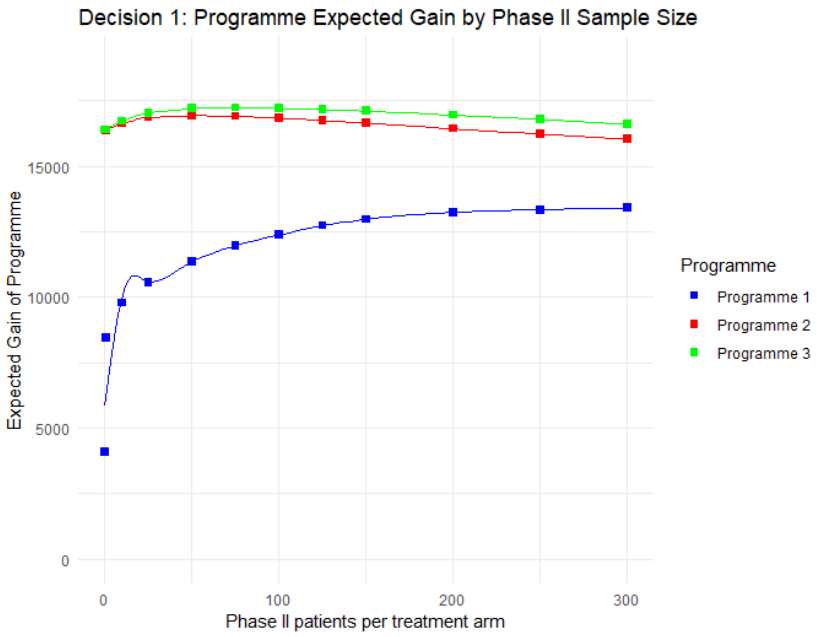

Figure 4-2: *Prior 2*: The expected gain over a range of different Phase II sample sizes. The standard error of each point estimate is less than 225. Due to the error coupling, the standard error between two estimates at the same n_1 but different programmes is roughly 150 for Programmes 1 and 2, 65 for Programmes 2 and 3.

Simulation Study Conclusions (Prior 2)

Prior 2 has mean for θ_i which are higher than Prior 1, so we see a shift upwards for the expected gain of all programmes. However the orderings and the maximising $n_1^{(t)}$ values remain similar. Note that in this case the optimal decision for Programme 1 based only on the prior (at $n_1^{(t)}$=0) is less fortuitously good as in Prior 1.

4.2.3 Case Study 2: The value of model selection in a Phase II/III programme

Case study setup

Suppose there are several candidate dose response relationships that may specify the relationship between the mean efficacy response at different doses. To model the uncertainty of the true relationship, we suppose the relationship may come from the following 5 dose response models with specified probabilities,

$$\begin{cases} q_1 & \boldsymbol{\mu} \text{ follows Emax}(\alpha_1, \alpha_2, \beta) \\ q_2 & \boldsymbol{\mu} \text{ follows Exp}(E_0, E_1, \delta) \\ q_3 & \boldsymbol{\mu} \text{ follows LinearLog}(E_0, E_1, c) \\ q_4 & \boldsymbol{\mu} \text{ follows Linear}(E_0, \delta) \\ q_5 & \boldsymbol{\mu} \text{ follows Quadratic}(E_0, \beta_1, \beta_2) \end{cases} \tag{4.8}$$

The probabilities q_1 to q_5 sum to one. The forms of these dose response models are given in Table 4.1. We suppose the parameters for each model have priors of the following form:

- Emax: $\boldsymbol{\alpha} \sim N(\mu_{\boldsymbol{\alpha}}, \Lambda_{\boldsymbol{\alpha}})$, $\beta \sim ln(\mu_\beta, \Lambda_\beta)$, where ln is a log-normal distribution.
- Exponential: $E_0 \sim N(\mu_{E_0}^{exp}, \Lambda_{E_0}^{exp})$, $E_1 \sim N(\mu_{E_1}^{exp}, \Lambda_{E_1}^{exp})$, $\delta \sim ln(\mu_\delta^{exp}, \Lambda_\delta^{exp})$.
- Linlog: $E_0 \sim N(\mu_{E_0}^{linlog}, \Lambda_{E_0}^{linlog})$, $E_1 \sim N(\mu_{E_1}^{linlog}, \Lambda_{E_1}^{linlog})$, $c \sim ln(\mu_c, \Lambda_c)$.
- Linear: $E_0 \sim N(\mu_{E_0}^{lin}, \Lambda_{E_0}^{lin})$, $\delta \sim N(\mu_\delta^{lin}, \Lambda_\delta^{lin})$.
- Quadratic: $E_0 \sim N(\mu_{E_0}^{quad}, \Lambda_{E_0}^{quad})$, $\beta_1 \sim N(\mu_{\beta_1}^{quad}, \Lambda_{\beta_1}^{quad})$, $\beta_2 \sim N(\mu_{\beta_2}^{quad}, \Lambda_{\beta_2}^{quad})$.

We study 4 programmes in this case study. Programmes 1-3 are of the same form specified in Case Study 1 but with different priors. In particular, Programme 3 uses an Emax$(\alpha_1, \alpha_2, \beta)$ model with priors for the parameters defined above. Programmes 1 and 2 assume the data follows a multivariate normal distribution with a diagonal and non-diagonal covariance matrix respectively, with the priors for the parameters derived from simulations from the true dose response relationship as in Case Study 1. Programme 4 is defined in the following way:

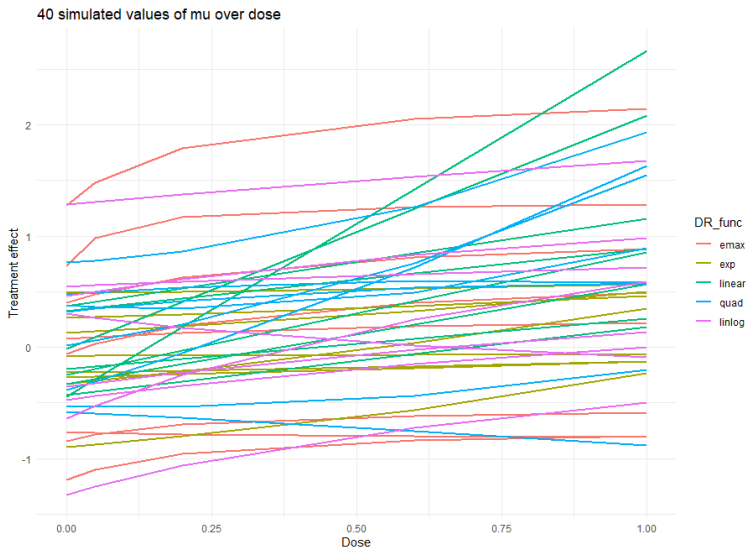

Figure 4-3: 40 simulated values of $\boldsymbol{\mu}$ using the probabilities in Equation 4.8 and the parameters to be defined below for this case study.

Programme 4 (MCP-Mod procedure to model $\boldsymbol{\mu}$)

- Specify a prior of the above form for each of the Emax, Exponential, Linear Log, Linear, and Quadratic model parameters.
- Given Phase II data $\boldsymbol{y}$, perform a multiple comparison procedure (MCP step) using appropriate *guesstimates* as discussed in Section 4.1.4.
- Using the model with the lowest p-value from the multiple comparison test, derive the posterior distribution $\boldsymbol{\mu}|\boldsymbol{y}$ from the posterior distributions of the parameters of the chosen model to make decisions in Decision 2.

Case study parameters

General parameters

As before, the 5 doses are $\boldsymbol{d} = (0, 0.05, 0.2, 0.6, 1.0)$ with $K = 5$. The standard deviation for responses is $\sigma = 3$. We use equal probabilities for each dose response model $q_1 = q_2 = q_3 = q_4 = q_5 = 0.2$.

Gain function parameters

$G = 35000$, $\gamma_1 = \gamma_2 = 1$, $\boldsymbol{S} = (0.9, 0.8, 0.75, 0.6)$.

Prior specification

- Emax: $\mu_{\boldsymbol{\alpha}} = (0, 0.5)$, $\Lambda_{\boldsymbol{\alpha}} = \text{diag}(0.5, 0.5)$, $\mu_\beta = -1$, $\Lambda_{\boldsymbol{\beta}} = \sqrt{0.6}$.
- Exponential: $\mu_{E_0}^{exp} = 0$, $\Lambda_{E_0}^{exp} = 0.5^2$, $\mu_{E_1}^{exp} = 0.5$, $\Lambda_{E_1}^{exp} = 0.5^2$, $\mu_\delta^{exp} = 1$, $\Lambda_\delta^{exp} = 0.5^2$.
- Linlog: $\mu_{E_0}^{linlog} = 0$, $\Lambda_{E_0}^{linlog} = 0.5^2$, $\mu_{E_1}^{linlog} = 0.5$, $\Lambda_{E_1}^{linlog} = 0.5^2$, $\mu_c = 0.5$, $\Lambda_c = 0.5^2$.
- Linear: $\mu_{E_0}^{lin} = 0$, $\Lambda_{E_0}^{lin} = 0.5^2$, $\mu_\delta^{lin} = 1$, $\Lambda_\delta^{lin} = 0.5^2$.
- Quadratic: $\mu_{E_0}^{quad} = 0$, $\Lambda_{E_0}^{quad} = 0.5^2$, $\mu_{\beta_1}^{quad} = 0.5$, $\Lambda_{\beta_1}^{quad} = 0.5^2$, $\mu_{\beta_2}^{quad} = 0.5$, $\Lambda_{\beta_2}^{quad} = 0.5^2$.

Figure 4-4 shows 40 dose response curves that are simulated from the above dose response relationships with the given priors.

Guesstimates for MCP step of MCP-Mod

Guesstimates are required for the multiple comparison contrast test for each model in Programme 4. We follow the original MCP-Mod framework and pick *guesstimates* according to the expected value of their prior distributions. Note that the log-normal parameterisation is such that if $\beta \sim ln(\mu, \sigma^2)$, then the expected value of β is $e^{\mu+\sigma^2/2}$.

- Emax: $\alpha = (0, 0.5)$, $\beta = e^{-1+0.6/2}$.
- Exponential: $E_0 = 0$, $E_1 = 0.5$, $\delta = e^{1+0.5/2}$.
- Linlog: $E_0 = 0$, $E_1 = 0.5$, $c = e^{1+0.5/2}$.
- Linear: $E_0 = 0$, $\delta = 1$.
- Quadratic: $E_0 = 0$, $\beta_1 = 0.5$, $\beta_2 = 0.5$.

Optimisation computations

As before, optimal decisions in Decision 2 are calculated over a discrete range of Phase III sample sizes N_2 using Monte Carlo simulation with 2000 simulations of realisations of the posterior distribution of the treatment effects $\boldsymbol{\theta}$ given the Phase II data. Optimal decisions in Decision 1 are calculated over Phase II sample sizes N_1 using Monte Carlo simulation with 1000 simulations of the true mean dose efficacy relationship $\boldsymbol{\mu}$.

In this simulation study, we use $N_1 := \{0, 1, 10, 25, 50, ..., 125, 150, 200, 250, 300\}$ and $N_2 := \{0, 200, 400, ..., 1800, 2000\}$ for Phase II and III respectively.

Results

Table 4.2: Table showing the percentage of times each model is the chosen model from the MCP-Mod procedure, depending on which true model the data is actually simulated from.

		MCP-Mod Chosen DR Model				
		Emax	Exponential	Linear	Quadratic	Linear Log
True DR	Emax	62.2	0	1.1	24.9	11.8
	Exponential	0	79.5	5.2	15.3	0
	Linear	0	0	97.6	2.4	0
	Quadratic	1.8	78.6	8.8	9.2	1.7
	Linear Log	5.7	0	78.3	16.0	0

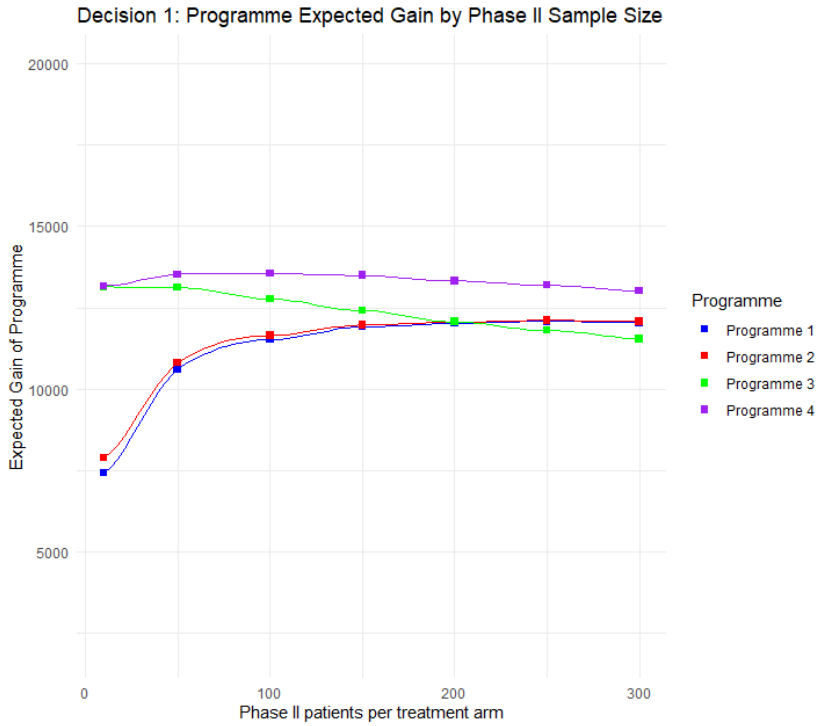

Figure 4-4: The expected gain over a range of different Phase II sample sizes. The standard error of each point estimate is less than 85. Due to the error coupling, the standard error between two estimates at the same n_1 but different programmes is roughly 30 for Programmes 1 and 2, 40 for Programmes 2 and 3, and 13 for Programmes 3 and 4.

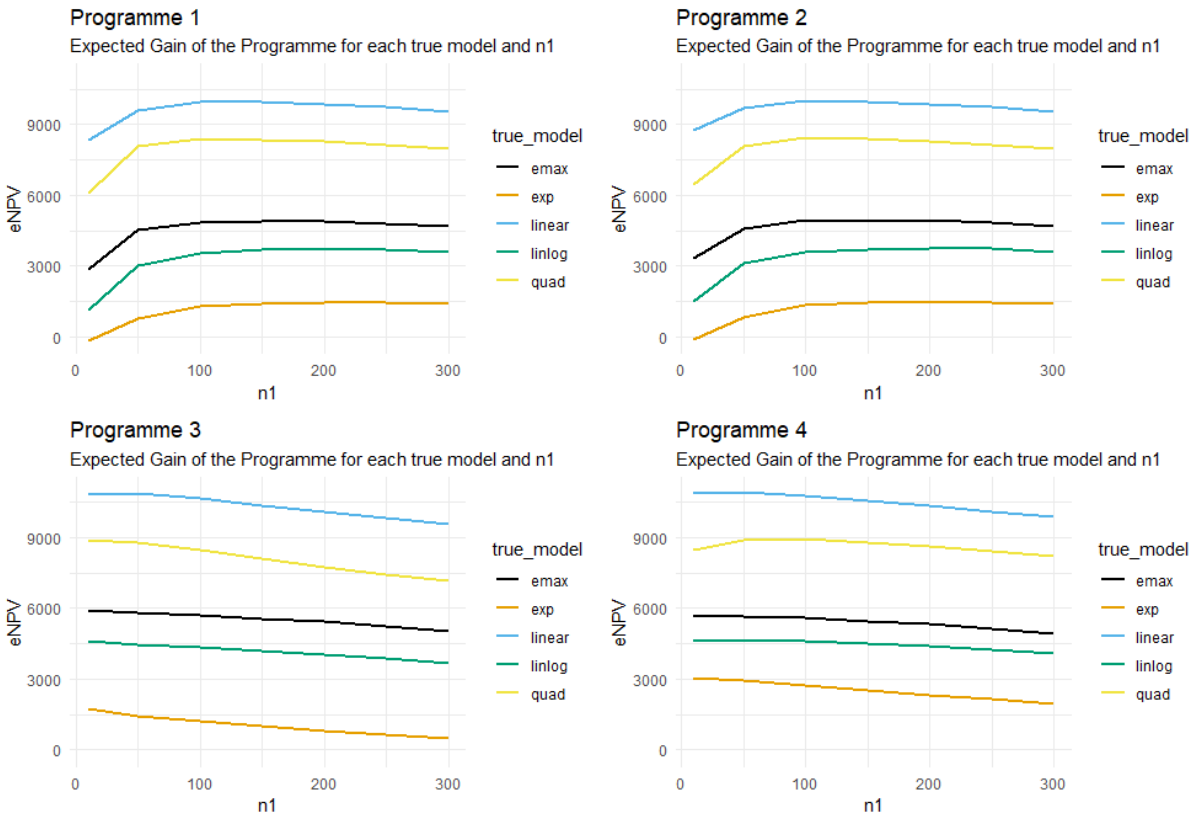

Figure 4-5: The expected gain of each programme depending upon the true dose response relationship and the Phase II sample size n_1.

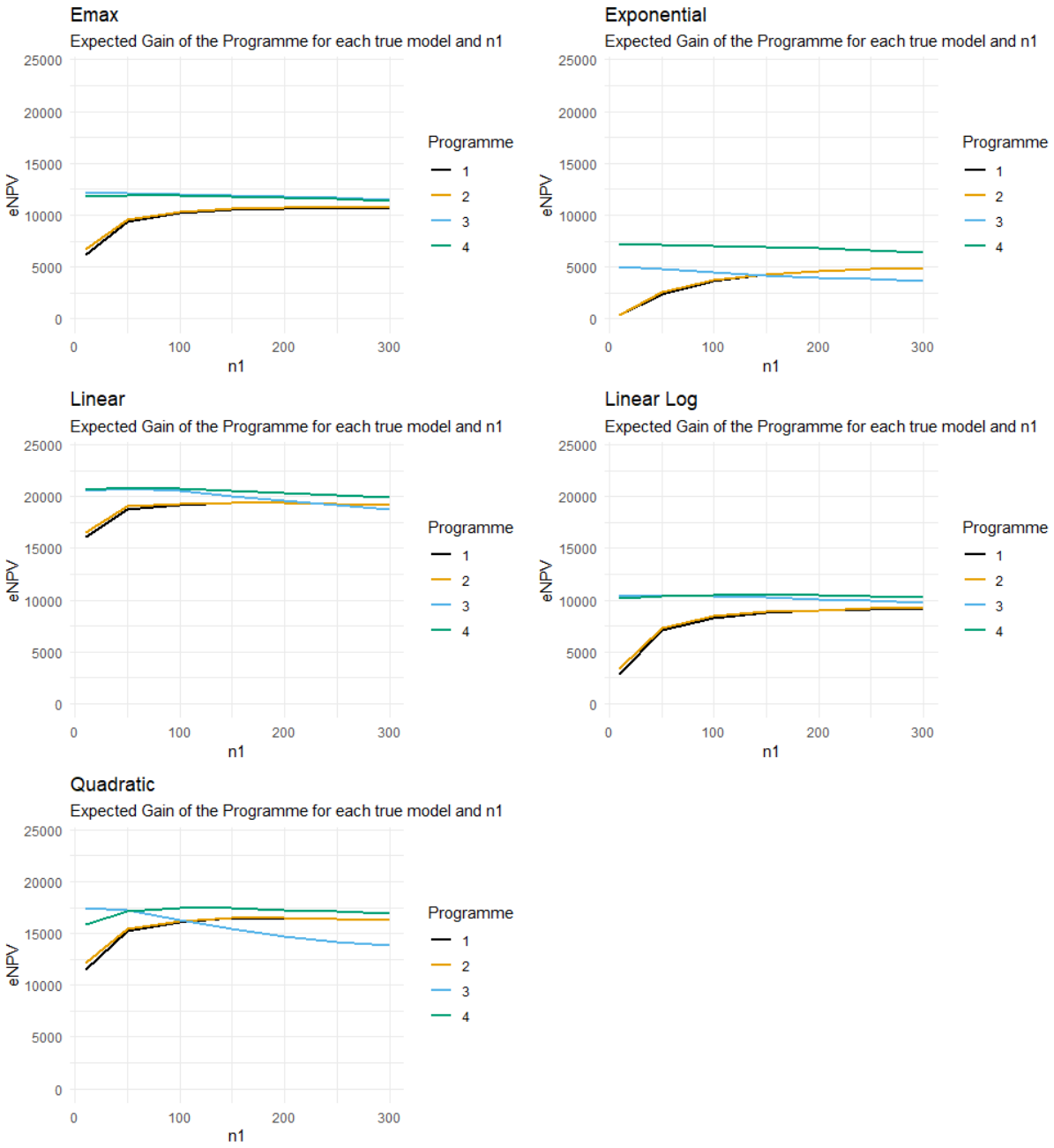

Figure 4-6: The expected gain of each programme depending given the true dose response relationship and the Phase II sample size n_1.

Simulation Study Conclusions

Comparing Programme Performances

Figure 4-4 shows that in most cases the order of Programmes is preserved, with each successive programme with more complex modelling procedures performing better than the last. In contrast to the previous simulation study (Case Study 1), there is not much difference between the performances of Programmes 3 and 4. Programmes 3 and 4 have low optimal values of Phase II sample size compared to Programmes 1 and 2 suggesting the more complex modelling procedures reduce the need for additional patients in Phase II.

Choosing the true model in Programme 4

Given the true dose response relationship, Programme 4 does not always identify the correct model in the MCP step of MCP-Mod as shown in Table 4.2.3. Subsets of a dose response

curve may be adequately modelled using another dose response curve. For example, the increasing part of a quadratic curve may be approximated using an exponential curve. It is not the aim to correctly identify the true dose response relationship, but rather to model the relationship adequately enough to make good decisions in Decision 2.

The linear log dose response relationship never gets correctly identified in Programme 4, and is instead identified as linear or quadratic. As mentioned above, this may be because linear or quadratic terms may approximate the linear log curve well on the subset of the curve the doses fall on. Secondly, the *guesstimates* used may lead to a contrast vector which is not very powerful for identifying a dose response relationship for many parameters of the linear log curve.

Programme 3 performs badly for large n_1

Figures 4-5 and 4-6 show how the expected gain depends upon the true underlying dose response relationship. The magnitude of expected gain of each relationship is driven primarily by the priors attached to the model parameters, with the linear model giving the most generous prior belief. Of interest is how the expected gains of each true relationship change across different programmes. One can see that for large values, Programme 3 performs poorly for quadratic and exponential forms of the true dose response relationship. This may be because these relationships produce true dose response curves that increase at a rate faster than linear which do not match up well with the Emax model with its specified choice of priors for its parameters. This low efficiency results in Programme 3 performing poorly for large values of n_1 in Figure 4-4.

Limitations

The effect of different prior distributions on the results has not been fully explored. For example, the results show much of the expected gain from the programme comes from a couple of dose response relationships (linear, quadratic) due to their prior distributions favouring efficacious treatments. In order to have a truly fair comparison, one would need the prior distributions for the parameters of each dose response relationship and corresponding weightings to represent the previous relationships between dose and responses that have entered Phase II clinical trials.

Sensitively analysis should be performed, changing parameters such as the potential financial gain G and the safety penalties, as these quantities cannot be fully known.

4.3 Discussion

Limitations of our approach

The safety penalties are an important part of the model and may be difficult to specify. Both simulation studies consider the trade-off between higher efficacy and greater safety considerations with a-priori known increasing safety penalties for each dose. In practice, it may be the case that the risk of adverse events or other safety considerations may only be known in the longer term, so applying penalties such as these may be the best one may hope for. However, the value of the programme and corresponding optimal decisions before Phase III depend highly upon these values. Whether these safety penalties are appropriate or not adds another layer of uncertainty to this problem.

In Case Study 2, Programme 4 becomes similar to a Bayes model selection routine (Raftery et al. (1997)). The difference in Programme 4 is that a single model is chosen based on the data, and posterior distributions are derived based upon this single model rather than an average over all of the models. Performing a hybrid frequentist-Bayesian routine is typical of approaches taken when a model selection routine is required due to the difficulties of performing a complete Bayes model averaging routine. Consider for example the family of models of k-component mixture distribution in Richardson and Green (1997) and the corresponding discussion from Jennison (1997). One must specify appropriate priors in this setting as dispersed priors for parameters carry a huge penalty for models with a large number of parameters. One must specify clear subjective prior distributions for parameters within each model which is difficult to obtain if there is uncertainty as to the correct model.

In neither of the case studies did we consider using adaptive methods to combine data from Phase II and III in the hypothesis test as in Programmes 2 and 4 and the use of group sequential designs as in Programmes 3 and 4 in Chapter 3. This would be a straightforward extension to the methodology studied here, and it is conjectured that these methods would add similar benefits to the programmes studied in this chapter. When generating the p-value for the Phase II data, this must be done as in Chapter 3 with no dose response relationship assumed. This is to avoid assumptions that the dose and mean efficacy response follow some parametric model influencing the hypothesis test.

Relevant current research

Design-focused procedures in current research can broadly be grouped into those which attempt to model the dose response relationship using parametric functions such as the $E_{\max}$ curve, and those which use semi-parametric or non-parametric methods to approximate it. Further distinctions are whether they use Bayesian methods or have a model selection routine. Our approach uses parametric functions and Bayesian methods.

Within the Bayesian literature, Thomas (2006) details a Bayesian parametric method for estimating the dose response curve, Bornkamp and Ickstadt (2009) and Grieve and Krams (2005) detail nonparametric Bayesian methods, and Müller et al. (2006) couple non-parametric Bayesian methods with adaptive designs. Nonparametric methods often must make assumptions such as monotonicity about the dose response curve due to the small number of doses (Kelly and Rice (1990)).

Another area of research includes adaptive dose allocation methods in Phase II, which is not considered in this chapter. Generally these approaches choose dose levels sequentially in order to minimise some measure of uncertainty about the dose response relationship. Two of these approaches are the General Adaptive Dose Allocation (GADA) and adaptive D-Optimal (D-Opt) designs. The GADA approach uses Bayesian decision theory to randomise each subject to placebo or a dose that results in the maximum increase in information about a measure relating to the dose response curve, such as the posterior probability of response at a target dose. The D-Opt approaches randomise each subject to a dose that minimises the variance of model parameters of a dose response curve. Some research (Bornkamp et al. (2007), Antonijevic et al. (2010)) has shown these to be more efficient in certain circumstances than design-focused procedures. Antonijevic et al. (2010) in particular evaluated the impact of dose selection strategies using programme-level measures, such as probability of Phase III success.

Summary

In this chapter, we have introduced the problem of dose response modelling in the context of Phase II clinical trials, and the MCP-Mod procedure for use under uncertainty of the correct dose response relationship. Two case studies were presented, the first quantifying the benefit to a Phase II/III programme of modelling dose and response with an Emax function, and the second quantifying the benefit to a Phase II/III programme of using the MCP-Mod procedure under uncertainty about the true dose response relationship.

Case Study 1 provides evidence of the value of using dose response modelling approaches in a Phase II/III programme. In particular, by not considering the dependency of different doses to one another, one may make poor decisions about the chosen dose and the sample size for the next phase within the programme, which may seriously affect the probability of identifying an efficacious dose and receiving revenue from the drug.

In Case Study 2, we found that using the full MCP-Mod framework added value to the programme under uncertainty about the true dose response relationship. The loss of value from using incorrect models (Programmes 1-3) was less than in the first simulation study, and decreased as n_1 became large.

In conclusion, whilst dose response modelling procedures have been compared before, and programme level analyses with financial model driven decision making have also been conducted before, the approach here to make financial model decision making in Phase II/III trials comparing different dose response procedures adds to current research. This research adds weight to the argument that using dose response modelling approaches can bring value to a Phase II/III programme.

Section 4 Appendices

4.A Sampling the posterior distribution of Emax model parameters

As detailed in the previous section, the Emax model is a popular choice for the dose response relationship. We detail below two approaches to sample from the posterior distribution of the model parameters.

4.A.1 The Neal (2003) MCMC slice sampling approach

Bornkamp, in the R package `DoseFinding` (Bornkamp et al. (2017)) suggests using slice sampling (Neal (2003)) as an efficient method for sampling from the posterior distribution of Emax model parameters. As an MCMC method, this method has the common drawbacks of MCMC methods, such as the need to show convergence.

4.A.2 The Temple (2012) rejection sampling approach

Temple (2012) takes a different approach, by using a 4 parameter Emax model with parameters $(\alpha_1, \alpha_2, \beta, h)$. A bivariate normal prior for $\boldsymbol{\alpha} = (\alpha_1, \alpha_2)$ and a prior for (β, h) is proposed and we assume the responses are normally distributed. Then in the posterior distribution of $(\boldsymbol{\alpha}, \beta, h)$ given observed data, the conditional distribution of $\boldsymbol{\alpha}$ given (β, h) is bivariate normal. This allows us to set up a algorithm which produces samples from the posterior distributions of each of $(\boldsymbol{\alpha}, \beta, h)$. One does this by sampling (β, h) from its marginal posterior distribution, then sampling $\boldsymbol{\alpha}$ from its conditional posterior distribution given (β, h).

We follow the Temple approach, but adapt it to consider the 3 parameter Emax model rather than the 4 parameter (sigmoid) Emax model (by dropping parameter h), as is used in Temple (2012). Below we note the derivation of the conditional posterior distributions of the model parameters, similarly to the one derived in Temple (2012).

Let the 3 parameter Emax model be defined by

$$f(z; \boldsymbol{\alpha}, \beta) = \alpha_1 + \alpha_2 \frac{z}{\beta + z}. \tag{4.9}$$

Let $y_{i,j}$ denote the ith observation on dose j. Suppose that the responses are

$$y_{i,j} = \alpha_1 + \alpha_2 \frac{z_j}{\beta + z_j} + \epsilon_{i,j}, \tag{4.10}$$

where $\epsilon_{i,j} \sim N(0,1)$ independently for $i = 1, ..., n_j$ and $j = 1, ..., K$. Then for the mean response on dose j, $\bar{Y}_j$, one may write

$$\bar{Y}_j \mid \boldsymbol{\alpha}, \beta \sim N(f(z_j; \boldsymbol{\alpha}, \beta), \sigma^2/n_j), \tag{4.11}$$

and the vector of mean responses $\bar{\boldsymbol{Y}}$ is distributed as

$$\bar{\boldsymbol{Y}} \mid \boldsymbol{\alpha}, \beta \sim N(X_\beta \boldsymbol{\alpha}, \Sigma), \tag{4.12}$$

where

$$X_\beta = \begin{bmatrix} 1 & \frac{z_1}{\beta + z_1} \\ \vdots & \vdots \\ 1 & \frac{z_J}{\beta + z_J} \end{bmatrix}, \quad \boldsymbol{\alpha} = \begin{bmatrix} \alpha_1 \\ \alpha_2 \end{bmatrix}, \tag{4.13}$$

and Σ is a $K \times K$ diagonal matrix with (k,k) entry $\sigma^2 n_k^{-1}$.

We specify a multivariate normal prior for $\boldsymbol{\alpha}$ as $\boldsymbol{\alpha} \sim N(\boldsymbol{\mu}_{\boldsymbol{\alpha}}, \Gamma_{\boldsymbol{\alpha}}^{-1})$ and denote the prior for β by $\pi_\beta(\beta)$. From Bayes' rule, the posterior distribution of the model parameters is

$$\pi_{\boldsymbol{\alpha},\beta|\boldsymbol{y}}(\boldsymbol{\alpha}, \beta|\boldsymbol{y}) \;\propto\; p_{\boldsymbol{y}}(\boldsymbol{y}|\boldsymbol{\alpha}, \beta)\pi_{\boldsymbol{\alpha}}(\boldsymbol{\alpha})\pi_\beta(\beta), \tag{4.14}$$

where the likelihood $p_{\boldsymbol{y}}(\boldsymbol{y}|\boldsymbol{\alpha}, \beta)$ is obtained from Equation 4.12. Noting that the likelihood $p_{\boldsymbol{y}}(\boldsymbol{y}|\boldsymbol{\alpha}, \beta)$ for the full data set $\boldsymbol{y}$ is proportional to the probability density function of vector of mean responses $p_{\bar{\boldsymbol{y}}}(\bar{\boldsymbol{y}}|\boldsymbol{\alpha}, \beta)$, we may write

$$\begin{aligned} \pi_{\boldsymbol{\alpha},\beta|\boldsymbol{y}}(\boldsymbol{\alpha}, \beta|\boldsymbol{y}) &\propto (2\pi)^{\frac{J+1}{2}} |\Sigma|^{-1/2} \exp(-\frac{1}{2}(\bar{\boldsymbol{y}} - X_\beta \boldsymbol{\alpha})^T \Sigma^{-1} (\bar{\boldsymbol{y}} - X_\beta \boldsymbol{\alpha})) \\ &\quad \times (2\pi)^{-1} |\Lambda_{\boldsymbol{\alpha}}|^{-1/2} \exp(-\frac{1}{2}(\boldsymbol{\alpha} - \boldsymbol{\mu}_{\boldsymbol{\alpha}})^T \Lambda_{\boldsymbol{\alpha}}^{-1} (\boldsymbol{\alpha} - \boldsymbol{\mu}_{\boldsymbol{\alpha}}))\; \pi_\beta(\beta) \\ &\propto \exp(-\frac{1}{2}(\boldsymbol{\alpha}^T (X_\beta^T \Sigma^{-1} X_\beta + \Lambda_{\boldsymbol{\alpha}}^{-1})\boldsymbol{\alpha} - 2\boldsymbol{\alpha}^T (X_\beta^T \Sigma^{-1} \bar{\boldsymbol{y}} + \Lambda_{\boldsymbol{\alpha}}^{-1} \boldsymbol{\mu}_{\boldsymbol{\alpha}})) \\ &\quad \times \exp(-\frac{1}{2}(\bar{\boldsymbol{y}}^T \Sigma^{-1} \bar{\boldsymbol{y}} + \boldsymbol{\mu}_\alpha^T \Lambda_{\boldsymbol{\alpha}}^{-1} \boldsymbol{\mu}_{\boldsymbol{\alpha}}))\; \pi_\beta(\beta). \end{aligned} \tag{4.15}$$

Define $\boldsymbol{\xi}_\beta := X_\beta^T \Sigma^{-1} \bar{\boldsymbol{y}} + \Lambda_{\boldsymbol{\alpha}}^{-1} \boldsymbol{\mu}_{\boldsymbol{\alpha}}$ and $\Delta_\beta := (X_\beta^T \Sigma^{-1} X_\beta + \Lambda_{\boldsymbol{\alpha}}^{-1})^{-1}$.

Then

$$\begin{aligned} \pi_{\boldsymbol{\alpha},\beta|\boldsymbol{y}}(\boldsymbol{\alpha}, \beta|\boldsymbol{y}) &\propto \exp(-\frac{1}{2}(\boldsymbol{\alpha} - \Delta_\beta \boldsymbol{\xi}_\beta)^T \Delta_\beta^T (\boldsymbol{\alpha} - \Delta_\beta \boldsymbol{\xi}_\beta)) \exp(\frac{1}{2} \boldsymbol{\xi}_\beta^{-1} \Delta_\beta \boldsymbol{\xi}_\beta) \pi_\beta(\beta) \\ &\propto \pi(\boldsymbol{\alpha}|\boldsymbol{y}, \beta) |\Delta_\beta|^{\frac{1}{2}} \exp(\frac{1}{2} \boldsymbol{\xi}_\beta^T \Delta_\beta \boldsymbol{\xi}_\beta) \pi_\beta(\beta). \end{aligned} \tag{4.16}$$

Therefore, we may extract the expressions for the conditional posterior distributions of $\boldsymbol{\alpha}$ and β as

$$\begin{aligned} \pi_{\beta|\boldsymbol{y}}(\beta|\boldsymbol{y}) &\propto |\Delta_\beta|^{\frac{1}{2}} \exp(\frac{1}{2} \boldsymbol{\xi}_\beta^T \Delta_\beta \boldsymbol{\xi}_\beta) \pi_\beta(\beta), \\ \boldsymbol{\alpha}|\boldsymbol{y}, \beta &\sim N(\Delta_\beta \boldsymbol{\xi}_\beta, \Delta_\beta) \end{aligned} \tag{4.17}$$

Thus to sample from the posterior distribution $\boldsymbol{\alpha}, \beta|\boldsymbol{y}$, we can sample β from the first equation and then sample $\boldsymbol{\alpha}$ from the second equation in Equations 4.17. Sampling β from $\beta|\boldsymbol{y}$ requires a form of rejection sampling. We describe this below.

To set up the rejection sampling,

- Denote $\pi_p(\beta|\boldsymbol{y}) := |\Delta_\beta|^{\frac{1}{2}}\exp(\frac{1}{2}\boldsymbol{\xi}_\beta^T\Delta_\beta\boldsymbol{\xi}_\beta)\pi_\beta(\beta)$ such that $\pi_{\beta|\boldsymbol{y}}(\beta|\boldsymbol{y}) \propto \pi_p(\beta|\boldsymbol{y})$.
- Split the domain on β up into discrete equally spaced intervals $(i_1, i_2), (i_2, i_3), ..., (i_{N_{\text{int}}-1}, i_{N_{int}})$.
- For interval $\mathfrak{I}_j := (i_j, i_{j+1})$, let $h_j := r \times \max(\pi_p(i_j|\boldsymbol{y}), \pi_p(i_{j+1}|\boldsymbol{y}))$.

The constant r should be large enough so that for $j = 1, ..., i_{N_{int}} - 1$, the maximum value of $\pi_\beta(\beta|\boldsymbol{y})$ in interval (i_j, i_{j+1}) is less than h_j. If there are enough intervals, a choice of $r = 1.1$ should be sufficient. For each simulation from the posterior distribution of β,

- Choose an interval $\mathfrak{I}'$ from $\mathfrak{I}_1, ..., \mathfrak{I}_{N_{\text{int}}-1}$ with probability proportional to $h_1, ..., h_{N_{\text{int}}-1}$.
- Choose $\beta_{\mathfrak{I}'}$ uniformly within this interval $\mathfrak{I}'$.
- With probability $\min(1, \pi_p(\beta_{\mathfrak{I}'}|\boldsymbol{y})/h_{\mathfrak{I}'})$ accept this $\beta_{\mathfrak{I}'}$. Otherwise, discard and choose another interval.

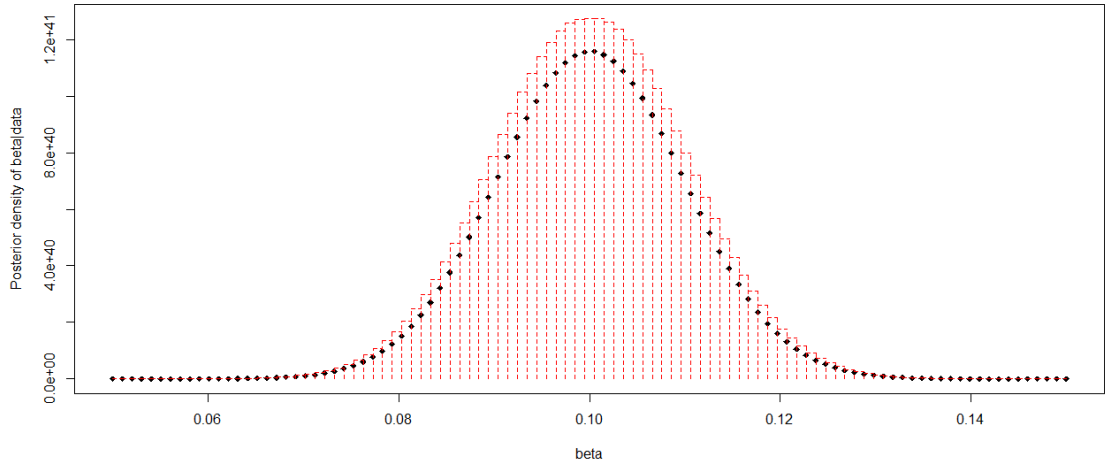

Figure 4-7: Rejection sampler algorithm. The rectangles are coloured in red with heights $h_1, ..., h_{N_{\text{int}}}$.

4.A.3 Methods for sampling from the posterior distribution of the parameters of other dose response functions

In this section we outline how the Temple rejection sampling method for finding the posterior of the parameters of an Emax model can be applied to other dose finding functions.

As for the Emax model case in Equation 4.12, we write

$$\bar{\boldsymbol{Y}}|\boldsymbol{\theta} \sim N(X\boldsymbol{\theta}, \Sigma) \tag{4.18}$$

where Σ is a $K \times K$ diagonal matrix with (k, k) entry $\sigma^2 n_k^{-1}$. The definitions of X and $\boldsymbol{\theta}$ depend upon the dose response model. We list the forms they take below

$$\text{Emax} \qquad X = \begin{bmatrix} 1 & e^{d_1/\delta} \\ \vdots & \vdots \\ 1 & e^{d_J/\delta} \end{bmatrix} \qquad \boldsymbol{\theta} = \begin{bmatrix} E_0 \\ E_1 \end{bmatrix}$$

$$\text{Power} \qquad X = \begin{bmatrix} 1 & d_1^{\delta} \\ \vdots & \vdots \\ 1 & d_J^{\delta} \end{bmatrix} \qquad \boldsymbol{\theta} = \begin{bmatrix} E_0 \\ E_1 \end{bmatrix}$$

$$\text{Linear} \qquad X = \begin{bmatrix} 1 & d_1 \\ \vdots & \vdots \\ 1 & d_J \end{bmatrix} \qquad \boldsymbol{\theta} = \begin{bmatrix} E_0 \\ \delta \end{bmatrix}$$

$$\text{Linear Log} \quad X = \begin{bmatrix} 1 & \log(d_1 + c) \\ \vdots & \vdots \\ 1 & \log(d_J + c) \end{bmatrix} \quad \boldsymbol{\theta} = \begin{bmatrix} E_0 \\ E_1 \end{bmatrix}$$

$$\text{Quadratic} \quad X = \begin{bmatrix} 1 & d_1 & d_1^2 \\ \vdots & \vdots & \\ 1 & d_J & d_J^2 \end{bmatrix} \qquad \boldsymbol{\theta} = \begin{bmatrix} E_0 \\ \beta_1 \\ \beta_2 \end{bmatrix}$$

The Emax, Power, and Linear Log dose response functions differ from the Linear and Quadratic dose response functions due to parameters in the nonlinear term of the dose response function.

As before, we define

$$\begin{aligned} \boldsymbol{\xi} &= X^T \Sigma^{-1} \bar{\boldsymbol{y}} + \Lambda_{\boldsymbol{\theta}}^{-1} \boldsymbol{\mu}_{\theta} \\ \Delta &= (X^T \Sigma^{-1} X + \Lambda^{-1})^{-1} \end{aligned} \tag{4.19}$$

In the Power, and Linear Log dose response function case, we have a similar form of expression to the Emax case in equation 4.17.

- Power

$$\begin{aligned} &\boldsymbol{\theta} | \boldsymbol{y}, \delta \sim N(\Delta \boldsymbol{\xi}, \Delta) \\ &\pi(\delta | \boldsymbol{y}) \propto |\Delta|^{1/2} \exp(\frac{1}{2} \boldsymbol{\xi}^T \Delta \boldsymbol{\xi}) \pi(\delta) \end{aligned} \tag{4.20}$$

- Linear Log

$$\begin{aligned} &\boldsymbol{\theta} | \boldsymbol{y}, c \sim N(\Delta \boldsymbol{\xi}, \Delta) \\ &\pi(c | \boldsymbol{y}) \propto |\Delta|^{1/2} \exp(\frac{1}{2} \boldsymbol{\xi}^T \Delta \boldsymbol{\xi}) \pi(c) \end{aligned} \tag{4.21}$$

Using these quantities, we follow the same method as in Section 4.A.2 by constructing an acceptance/rejection sampling algorithm to sample the parameter in the nonlinear term (δ or c).

For the Linear and Quadratic case, the process becomes simple as there is no parameter in the nonlinear term one needs to sample from. Thus we may sample directly from the posterior distribution of all the model parameters;

$$\boldsymbol{\theta}|\boldsymbol{y} \sim N(\Delta\boldsymbol{\xi}, \Delta). \tag{4.22}$$

4.B MCP-Mod

We specify the classical MCP-Mod Approach as in the original Bornkamp (2006) paper.

Consider the model

$$y_{i,j} = \mu(d_i) + \epsilon_{i,j}, \quad \epsilon_{i,j} \overset{\text{iid}}{\sim} N(0, \sigma^2), \tag{4.23}$$

for $i = 1, ..., K$, and $j = 1, ..., n_i$. Thus, the observed response $y_{i,j}$ for patient j at dose d_i is normally distributed with a known homogeneous variance across all doses, and the mean response for a particular dose d_i is given by $\mu(d_i)$. We suppose the dose response model with parameters $\boldsymbol{\theta}$ specifies $\mu(d_i) = f(d_i, \boldsymbol{\theta})$. Denote by $\boldsymbol{\mu}$ the vector of mean responses $(\mu(d_1), ..., \mu(d_K))^T$.

The MCP-Mod procedure can be separated into two stages. The multiple comparison procedure stage (MCP), and the inference from the fitted model stage (Mod).

MCP Stage

One starts by specifying M candidate models. Each model can be expressed in the form

$$f(d, \boldsymbol{\theta}) = \theta_0 + \theta_1 f^0(d, \boldsymbol{\theta}^0) \tag{4.24}$$

where $f^0(d, \boldsymbol{\theta}^0)$ is the standardised version of $f(d, \boldsymbol{\theta})$. Table 4.1 gives a selection of commonly used dose response models with their standardised counterparts.

As part of the model selection multiple comparison step, we test null hypotheses $H_0^m : \boldsymbol{c}_m^T\boldsymbol{\mu} = 0$ for $m = 1, ..., M$ where m are indices for particular models. These are tested against the one-sided alternatives $H_0^m : \boldsymbol{c}_m^T\boldsymbol{\mu} > 0$ for a given set of contrast vectors $\boldsymbol{c}_m = (c_{m,1}, ..., c_{m,K})^T$ which satisfy $||\boldsymbol{c}_m||_1 = 0$ for each $m = 1, ..., M$, where $||\boldsymbol{c}_m|| := \sum_{i=1}^K c_{m,i}$. Single contrast test statistics can be defined by

$$Z_m = \frac{\boldsymbol{c}_m^T\bar{\boldsymbol{Y}}}{\sqrt{\sigma^2 \sum_{i=1}^k c_{m,i}^2/n_i}}, \tag{4.25}$$

for $m = 1, ..., M$ where $\bar{\boldsymbol{Y}} = (\bar{Y}_1, ..., \bar{Y}_K)'$ and $\bar{Y}_i$ is the mean response for dose $i = 1, ..., K$. Note that under H_0^m, $Z_m \sim N(\tau(\boldsymbol{c}_m), 1)$, where the non-centrality parameter $\tau(\boldsymbol{c}_m) = \boldsymbol{c}_m^T\boldsymbol{\mu}/(\sigma^2 \sum_{i=1}^K c_{m,i}^2/n_i)^{1/2}$.

An optimal contrast may be defined as a vector $\boldsymbol{c}$ that maximises $\tau(\boldsymbol{c})$ given a particular model function $f(d, \boldsymbol{\theta})$. In order to find this, $\boldsymbol{\mu}$ must be specified which requires the parameter vector $\boldsymbol{\theta}$ to be specified. We refer to *Guesstimates* as values of $\boldsymbol{\theta}$ chosen in order to derive optimal contrasts. Optimal contrasts $\boldsymbol{c}_m$ maximise $\tau(\boldsymbol{c}_m)$ for *guesstimates* $\boldsymbol{\theta}$. In Bretz et al. (2005), the optimal contrasts for model selection are shown to be invariant to any shift and scale change in the mean response vector. Thus, optimal contrasts for a model are the same as the optimal contrasts for the standardised version of that model.

As in Bretz and Xun (2017), the optimal contrasts take the form

$$c_i \ \propto \ n_i(\mu_i - \bar{\mu}), \tag{4.26}$$

for $i = 1, ..., K$, where $\bar{\mu} = \sum_{i=1}^{K} n_i\mu_i / \sum_{i=1}^{K} n_i$. We then require $\sum_{i=1}^{K} c_i^2 = 1$.

In the multiple comparison test under the null hypothesis, the test statistics $\boldsymbol{Z} := \{Z_1, ..., Z_M\}$ follow a central multivariate normal distribution with a covariance matrix R which depends on the sample sizes and contrast coefficients, which is derived in Appendix 4.C.

Any dose response model with a test statistic larger than $q_{1-\alpha}$ can be declared statistically significant under the contrast test at level α, where $q_{1-\alpha}$ is defined as the multiplicity-adjusted critical value such that the probability of $\max(\boldsymbol{Z}) \geq q_{1-\alpha}$ under the null hypothesis is equal to α. This can be written as

$$\begin{aligned} \mathbb{P}(\max(\boldsymbol{Z}) \geq q_{1-\alpha} \mid \boldsymbol{\mu}_0 = \boldsymbol{0}) &= 1 - \mathbb{P}(\max(\boldsymbol{Z}) \leq q_{1-\alpha} \mid \boldsymbol{\mu}_0 = \boldsymbol{0}) \\ &= 1 - \mathbb{P}(\boldsymbol{Z} \leq (q_{1-\alpha}, ..., q_{1-\alpha}) \mid \boldsymbol{\mu}_0 = \boldsymbol{0}) \end{aligned} \tag{4.27}$$

These critical values can be computed using software which computes the cumulative density function of multivariate normal random variables, such as the `mvtnorm` package (Genz et al. (2008)). The non-centrality parameter for the joint distribution is $\boldsymbol{\delta}_m := (\delta_{m,1}, ...\delta_{m,M})$, with

$$\delta_{m,l} = \boldsymbol{c}_m'\boldsymbol{\mu}_m / (\sigma^2 \sum_{i=1}^{K} c_{m,i}^2 / n_i)^{1/2} \tag{4.28}$$

The power of the test to detect the dose response relationship is the probability of detecting the dose response under a model with responses $\boldsymbol{\mu}_m$ and is written as

$$\begin{aligned} p^*_{\boldsymbol{\mu}=\boldsymbol{\mu}_m; q_{1-\alpha}} &:= \mathbb{P}(\max(\boldsymbol{Z}) \geq q_{1-\alpha} \mid \boldsymbol{\mu} = \boldsymbol{\mu}_m) \\ &= 1 - P(Z_1 < q_{1-\alpha}, ..., Z_M < q_{1-\alpha} \mid \boldsymbol{\mu} = \boldsymbol{\mu}_m) \\ &= 1 - P(\boldsymbol{Z} < (q_{1-\alpha}, ..., q_{1-\alpha}) \mid \boldsymbol{\mu} = \boldsymbol{\mu}_m). \end{aligned} \tag{4.29}$$

Mod Stage

The best model is selected according to the multiplicity adjusted p-values from the contrast test or AIC/BIC criteria. The dose response model is then used to estimate target doses according to some criterion. In the original method, this is the minimum effective dose, but other approaches may be used.

4.C Correlation matrix derivation for $\boldsymbol{Z}$

Firstly we note

$$Z_l = \frac{\boldsymbol{c}_l^T \bar{\boldsymbol{Y}}}{\sqrt{\sigma^2 \sum_{i=1}^{k} c_{l,i}^2 / n_i}} \tag{4.30}$$

is distributed as a $N(\tau_l, 1)$ distribution, where

$$\tau_l = \frac{\boldsymbol{c}_l^T \boldsymbol{\mu}}{\sqrt{\sigma^2 \sum_{i=1}^{k} c_{l,i}^2 / n_i}}. \tag{4.31}$$

Writing the statistic in this form allows us to deduce that Z_l is distributed as a distribution with non-centrality parameter τ_l.

Consider now the multivariate statistic

$$\boldsymbol{Z} = (Z_1, ..., Z_M) = \left(\frac{\boldsymbol{c}_1^T \bar{\boldsymbol{Y}}}{\sqrt{\sigma^2 \sum_{i=1}^k c_{1,i}^2 / n_i}}, ..., \frac{\boldsymbol{c}_M^T \bar{\boldsymbol{Y}}}{\sqrt{\sigma^2 \sum_{i=1}^k c_{M,i}^2 / n_i}} \right). \tag{4.32}$$

From this, the non-centrality parameter may be read off as $\boldsymbol{\delta} = (\delta_1, ..., \delta_M)$ where

$$\delta_l = \frac{\boldsymbol{c}_l^T \boldsymbol{\mu}}{\sqrt{\sigma^2 \sum_{i=1}^k c_{l,i}^2 / n_i}} \text{ for } l = 1, ..., M. \tag{4.33}$$

The degrees of freedom are again ν. The correlations can be found by

$$\begin{aligned} \rho_{\tilde{i},\tilde{j}} &= \text{Corr} \left(\frac{\boldsymbol{c}_{\tilde{i}}^T \bar{\boldsymbol{Y}}}{\sqrt{\sigma^2 \sum_{i=1}^k c_{\tilde{i},i}^2 / n_i}}, \frac{\boldsymbol{c}_{\tilde{j}}^T \bar{\boldsymbol{Y}}}{\sqrt{\sigma^2 \sum_{i=1}^k c_{\tilde{j},i}^2 / n_i}} \right) \\ &= \frac{1}{\sqrt{\sigma^2 \sum_{i=1}^k c_{\tilde{i},i}^2 / n_i}} \frac{1}{\sqrt{\sigma^2 \sum_{i=1}^k c_{\tilde{j},i}^2 / n_i}} \sum_{k=1}^M c_{\tilde{i},k} c_{\tilde{j},k} \text{Var}(\bar{Y}_K) \sigma^2 / n_k \\ &= \frac{\sum_{k=1}^K c_{\tilde{i},k} c_{\tilde{j},k} / n_k}{\sqrt{\sum_{k=1}^K c_{\tilde{i},k}^2 / n_k \sum_{k=1}^K c_{\tilde{j},k}^2 / n_k}}. \end{aligned} \tag{4.34}$$

4.D Adaptations to the MCP-Mod procedure

The methodology introduced in Bretz et al. (2005) has been subject to several extensions, such as the extension to general parametric models in Pinheiro et al. (2014). This means that the methodology can be used for Cox proportional hazard models, linear mixed effect models, and generalised nonlinear models. The main restriction is that the dose and response are both univariate. We outline the generalisation below.

Suppose y is the response of a patient receiving dose d, and write the model as

$$y \sim F(\mu(d), \boldsymbol{z}, \boldsymbol{\eta}), \tag{4.35}$$

where $\mu(d)$ is the dose response relationship, $\boldsymbol{z}$ covariates, and $\boldsymbol{\eta}$ nuisance parameters. The same approach is taken, with a multiple contrast test and dose response modelling performed.

Suppose M candidate models with mean responses $\boldsymbol{\mu}_1, ..., \boldsymbol{\mu}_M$ are specified, and an optimal contrast found for each. These take the form

$$\boldsymbol{c}_m^{\text{opt}} \propto S^{-1} \left(\boldsymbol{\mu}_m - \frac{\boldsymbol{\mu}_m S^{-1} \mathbb{1}}{\mathbb{1}' S^{-1} \mathbb{1}} \right) \quad \forall m, \tag{4.36}$$

where S is the covariance matrix of the estimated dose response parameters $\hat{\boldsymbol{\mu}}$.

In the MCP stage, estimates $\hat{\boldsymbol{\mu}}$ and $\hat{S}$ are found by fitting an appropriate model with doses as a factor. The contrast test statistic is defined as

$$z_m = (\boldsymbol{c}_m^{\text{opt}})^T \hat{\boldsymbol{\mu}} / \sqrt{(\boldsymbol{c}_m^{\text{opt}})^T \hat{S} (\boldsymbol{c}_m^{\text{opt}})} \quad \forall m. \tag{4.37}$$

In a lot of scenarios, $\hat{\boldsymbol{\mu}}$ is asymptotically multivariate normal. Thus, suitable models may then be used for the Mod stage as before.

König (2015) extends the methodology to allow individual pairwise dose control comparisons in the MCP step, and adaptive interim analyses using combination tests which allow one to change models, sample sizes, or doses.

Bretz and Xun (2017) provides an overview of practical considerations involved when using MCP-Mod methodology, as well as an introduction to the DoseFinding R package Bornkamp et al. (2010).

4.D.1 Improving the optimal contrasts in a Bayesian setting by removing *guesstimates*

Suppose that we attach a prior to the parameters $\boldsymbol{\theta}$ of each model denoted by $\pi_0(\boldsymbol{\theta})$.

In this setting, we may calculate the optimal contrasts $\boldsymbol{c}$ for each model m so that they maximise the following *average power over the prior* objective function,

$$I_m(\boldsymbol{c}) := \int_{\boldsymbol{\theta}} p^*_{\boldsymbol{\mu}=\boldsymbol{\mu}_m(\theta)} \pi_0(\boldsymbol{\theta}) d\boldsymbol{\theta} \tag{4.38}$$

This will take into account the uncertainty about the exact shape of the model rather than relying on a specific case obtained from *guesstimates*. This comes at the cost of having to specify prior distributions for the model parameters, which may be difficult if there is little information about possible dose response effects. However, in situations where inference is to be performed later using Bayesian methods, these will need to be specified anyway.

Computations

Bretz et al. (2005) describe an algorithm for finding the optimal contrasts that maximise $\tau(\boldsymbol{c})$. We may simply adapt this algorithm to find the contrasts that maximise any objective function; in particular $I(\boldsymbol{c})$, instead of $\tau(\boldsymbol{c})$. We outline this algorithm below.

The algorithm uses parameterisations to reduce the constrained optimisation of $I(\boldsymbol{c})$ subject to $||\boldsymbol{c}||_1 = 0$ and $||\boldsymbol{c}||_2 = 1$ to an unconstrained problem, which is easier to solve computationally using standard optimisation software. The algorithm is as follows:

Find $\delta_2, ..., \delta_{K-1} \in \mathbb{R}^{K-2}$ which maximise $I(\boldsymbol{c})$, where $\boldsymbol{c}$ is found from $\delta_2, ..., \delta_{K-1}$ in the following way:

$$\begin{aligned} c_i &= \sin(\gamma_i) \prod_{j=1,...,i-1} \cos(\gamma_i), \text{ for } i = 1, ..., K-1 \\ c_K &= \prod_{j=1,...,K-1} \cos(\gamma_j), \end{aligned} \tag{4.39}$$

where $\gamma_1, ..., \gamma_K$ are found from

$$\begin{aligned} \gamma_i &= -\pi/2 + \pi/(1 + \exp(-\delta_i)), \text{ for } i = 2, ..., K \\ \gamma_1 &= \tan^{-1}\left(- \left(\sum_{i=1,...,K-1} \sin(\gamma_i) \prod_{j=2,...,i-1} \cos(\gamma_j) \right) - \prod_{j=2,...,K-1} \cos(\gamma_j) \right). \end{aligned} \tag{4.40}$$

Note that first parameterisation of $c_1, ..., c_K$ in terms of $\gamma_1, ..., \gamma_{K-1}$ maps the elements of the

contrast vector onto the surface of a unit sphere, which forces the condition $||\boldsymbol{c}||_2 = 1$ at the expense of one degree of freedom. The $||\boldsymbol{c}||_1 = 0$ condition is forced by stipulating γ_1 takes the form above as a function of $\gamma_2, ..., \gamma_{K-1}$ at the expense of a further degree of freedom. Then $\gamma_2, ..., \gamma_{K-1}$ may be chosen freely in $[-\pi/2, \pi/2]$ to maximise the objective function. The last parameterisation of $\gamma_2, ..., \gamma_{K-1}$ in terms of $\delta_2, ..., \delta_{K-1}$ makes the optimisation unconstrained. That is, $\delta_2, ..., \delta_{K-1}$ may be chosen in $\mathbb{R}^{K-2}$ to optimise $I(\boldsymbol{c})$ using standard optimisation software.

Benefits of the Approach

The benefits of using the approach described here are marginal in terms of the increase in $\mathcal{I}_m(\boldsymbol{c})$. We illustrate this in the following simulation study.

Suppose one suspects the dose response relationship follows an exponential model ($\text{Exp}(E_0, E_1, \delta)$) with some uncertainty associated with the parameter of the distribution. In particular, suppose the parameter δ has a Gamma$(4, 4)$ prior distribution. 50 realisations of the exponential model where the parameter δ has been sampled from this, and other priors, are shown in Figure 4-8.

The optimal contrast vector $\boldsymbol{c}$ vector for each case may be found using the guesstimate approach (Optimisation from *guesstimate*) as in Bretz et al. (2005), or using our approach, where the optimal $\boldsymbol{c}$ is found to maximise Equation 4.38 (Optimisation from prior). The doses used were $(0, 0.05, 0.2, 0.6, 1)$ with a sample size of 80 per dose. In Table 4.3, the optimal $\boldsymbol{c}$ is displayed for each method accompanied with the corresponding value of $I(\boldsymbol{c})$ and power of the test at the guesstimate. We compare the contrast finding methods in terms of their corresponding $I(\boldsymbol{c})$ values. The *guesstimates* used are $\delta = 1$ for the exponential model, and $\beta = 2/3$, $h = 2/3$ for the gamma model.

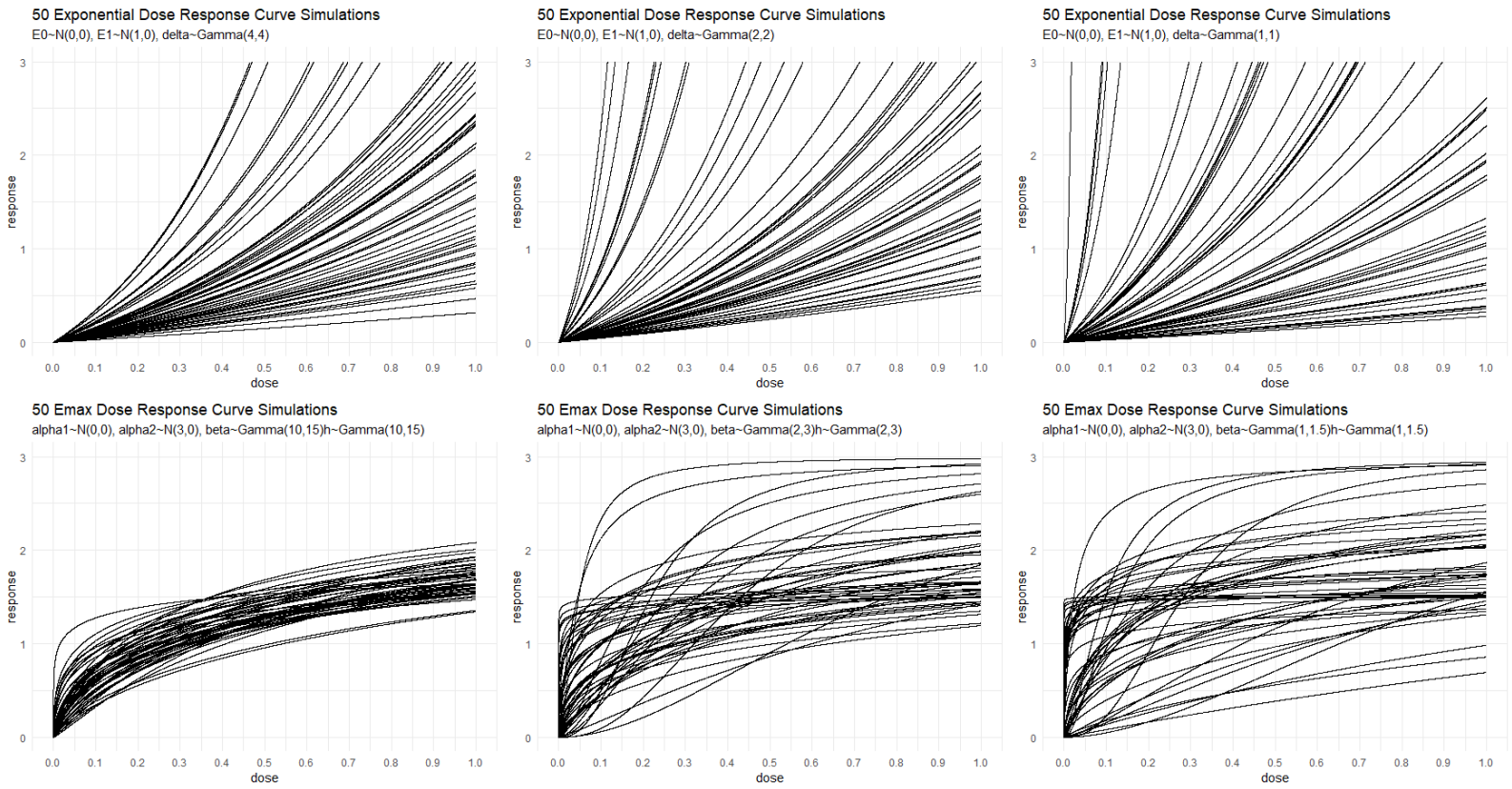

Figure 4-8: 50 realisations of the exponential model where the parameter δ has been sampled from different prior distributions and the sigmoid Emax model where the parameters β, h have been sampled from different prior distributions.

Table 4.3: Gain in power and $I_m(\boldsymbol{c})$ when finding the contrasts from the prior distribution compared to finding them from the *guesstimates*.

Model	Parameter Prior	Contrast Finding Method	Contrast $\boldsymbol{c}$	Power at guesstimate	$I_m(\boldsymbol{c})$
Exp(λ)	$\lambda \sim$ Gamma$(4,4)$	Optimisation from *guesstimate*	(-0.389, -0.353, -0.236 ,0.180, 0.797)	99.054%	88.217%
		Optimisation from prior	(-0.402, -0.361, -0.227, 0.207, 0.783)	99.047%	88.233%
	$\lambda \sim$ Gamma$(2,2)$	Optimisation from *guesstimate*	(-0.389, -0.353, -0.235, 0.180, 0.798)	99.054%	84.600%
		Optimisation from prior	(-0.405, -0.362, -0.226, 0.211, 0.781)	99.045%	84.620%
	$\lambda \sim$ Gamma$(1,1)$	Optimisation from *guesstimate*	(-0.389, -0.353, -0.235, 0.180, 0.798)	99.054%	78.086%
		Optimisation from prior	(-0.477, -0.432, 0.000, 0.162, 0.748)	98.586%	82.391%
sigEmax(β, h)	$\beta, h \sim$ Gamma$(10,15)$	Optimisation from *guesstimate*	(-0.648, -0.324, 0.016, 0.387, 0.569)	95.578%	71.316%
		Optimisation from prior	(-0.670, -0.299, 0.0237, 0.384, 0.561)	95.557%	71.371%
	$\beta, h \sim$ Gamma$(2,3)$	Optimisation from *guesstimate*	(-0.648, -0.324, 0.016, 0.387, 0.569)	95.578%	67.832%
		Optimisation from prior	(-0.730, -0.222, 0.054, 0.369, 0.529)	95.216%	68.799%
	$\beta, h \sim$ Gamma$(2/3,1)$	Optimisation from *guesstimate*	(-0.648, -0.324, 0.016, 0.387, 0.569)	95.578%	64.752%
		Optimisation from prior	(-0.778, -0.149, 0.086, 0.350, 0.491)	94.454%	67.649%

From this table, one can draw the conclusions that when there is a moderate amount of uncertainty as to the parameter of the Emax model, finding the contrasts using this method is always slightly, but not significantly, better than finding it using *guesstimates*. However, in the case where there is a large amount of uncertainty (such as Gamma$(1, 1)$ for the Exponential and $\beta, h \sim$ Gamma$(2/3, 1)$ for the sigmoid Emax, there is a significant improvement of a few percentage points.

One may ask where this improvement comes from, in terms of which dose response curves are now found significant with the contrast obtained from our new method where they were not previously with the contrast obtained from the *guesstimate*. It is possible it is the case that this improvement comes from dose response curves which are not promising in terms of efficacy, in which case the increase in power may not be so important. Further work could be done by specifying the relative importance of detecting a dose response relationship for different dose response curves in the objective function.

This simulation shows that with appropriate guesstimates, the gain obtained by choosing the contrast vectors optimally according to the prior is minimal.

4.E Interpretation of the Prior 1 and 2

In Figure 4-9, we plot simulated dose response curves given the priors used in Case Study 2 and list the properties of these simulated dose response curves in Table 4.4.

Table 4.4: Properties of the 3 priors

	Prior 1	*Prior 2*
$P(\alpha_1 > 0)$	0.5	0.5
$P(\alpha_2 > 0)$	0.760	0.837
mean β	0.199	0.440
mean θ	(0.01, 0.16, 0.29, 0.39, 0.43)	(0.00, 0.19, 0.41, 0.63, 0.73)
$P(\theta_K - \theta_1 > 0)$	0.693	0.791
$P(\theta_K - \theta_1 > 0.25)$	0.580	0.695
$P(\theta_K - \theta_1 > 0.5)$	0.460	0.585
$P(\theta_K - \theta_1 > 0.75)$	0.346	0.475
$P(\theta_K - \theta_1 > 1)$	0.242	0.370

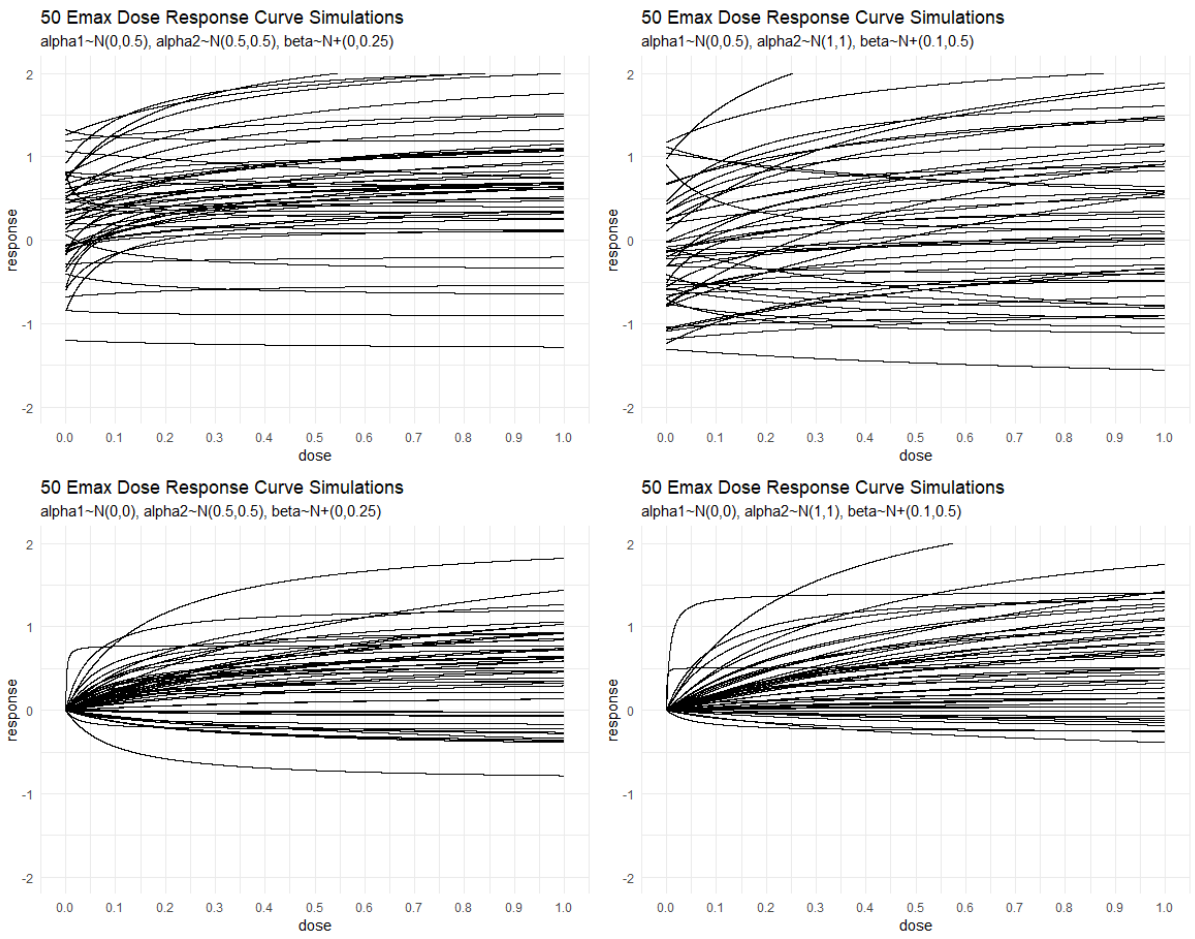

Figure 4-9: Plots of 50 samples from the prior distribution (top), and those same samples translated so that they start at the origin (bottom).

5

Multiple Phase III Trials

5.1 Introduction

Whilst it is not necessary in all cases, typically one would expect there to be two successful Phase III trials in order to demonstrate a new treatment's safety and efficacy, in order to obtain approval from the regulatory agencies such as the FDA or EMA; see for example Aksamit et al. (2017), Simpson et al. (2016), or Kimball et al. (2016). In the previous chapters, we have considered programmes consisting of only a single Phase III trial. Previous literature focusing on Phase II/III programmes has generally not considered more than one Phase III design.

We assume both Phase III trials must be successful in order for the treatment to be marketed. From a statistical modelling point of view, one may ask for the reasoning behind having two independent Phase III trials? Suppose one has two Phase III trials with type I error rate α. An argument may be that it is more efficient to perform one larger Phase III design with type I error rate α^2. The reasons why having two Phase III trials may be preferred may be due to the the rigidity of the assumptions one uses when performing statistical modelling. Two separate trials may be performed over different centres with different trial managers. Pooling the patients together in one centre with the same trial manager will mean the administrative methods used to execute the trial will be homogeneous, meaning any inherent bias in the methods (such as the pool from which the subjects are recruited) will bias the whole of Phase III. Having two Phase III trials aims to reduce this.

In this section we consider the problem of having two Phase III trials. In particular, the question of when to perform each Phase III trial, and if they are group sequential, which boundaries are optimal. We denote the two Phase III trials as Phase IIIa and Phase IIIb.

We take a similar approach to Chapter 3 and 4 by performing studies to assess the value of different approaches to performing Phase II/III programmes with two Phase III trials. In Section 5.1.1 we list the new notation used in this Chapter, in Section 5.1.2 we define the gain function, and in Section 5.1.3, we motivate the simulation studies to be performed.

5.1.1 Notation

We adapt some notation for this chapter from those in Chapters 3 and 4.

n_1 := The sample size per treatment in Phase II.

n_2 := The sample size per treatment in Phase IIIa.

n_3 := The sample size per treatment in Phase IIIb.

$\hat{\theta}_1$:= the maximum likelihood estimate of the treatment effect based on Phase II data.

$\hat{\theta}_2$:= the maximum likelihood estimate of the treatment effect based on Phase IIIa data.

$\hat{\theta}_3$:= the maximum likelihood estimate of the treatment effect based on Phase IIIb data.

γ_1 := Cost of a Phase II patient ($\gamma_1 > 0$).

γ_2 := Cost of a Phase IIIa or IIIb patient ($\gamma_2 > 0$).

$\mathfrak{I}_0 := (\sigma^2, G, \gamma_1, \gamma_2, \theta_0, \Sigma_0)$ the set of global parameters known at the beginning of the programme. θ_0 and Σ_0 are parameters for the prior distribution of the treatment effect θ.

$\mathfrak{I}_1 := (\mathfrak{I}_0, \hat{\theta}_1)$, the set of cumulative summary statistics formed from $\mathfrak{I}_0$ plus summary statistics from Phase II.

N_1, N_2, N_3 := Vectors of possible sample sizes for Phase II, IIIa, and IIIb respectively.

We also introduce notation for the financial model gain function

T_{pat} := The patent time remaining at the start of the setup of Phase II.

$G(t, T_{\text{pat}})$:= Function for the revenue rate at time t measured from the start of Phase II when the patent life is T_{pat}.

ρ := Parameter concerning the annual inflation rate such that 1 unit of currency today is worth $e^{-\rho}$ after one year.

c := Parameter concerning the exponential decay in revenue after the patent expires.

$T_{\text{PhII setup}}$:= The time required to set up Phase II.

$T_{\text{PhIII setup}}$:= The time required to set up the pair of Phase III trials.

$T_{\text{PhII pat}}$:= The time required to recruit a patient in Phase II.

$T_{\text{PhIII pat}}$:= The time required to recruit a patient in Phase III.

$\gamma_{\text{PhII overhead}}$:= The overhead cost of starting a Phase II trial.

$\gamma_{\text{PhIII overhead}}$:= The overhead cost of starting a Phase III trial.

5.1.2 Financial model gain function

Time is of particular importance in the two Phase III problem. The choice as to when to perform each Phase III trial may become a trade off between investing money up front to finish the trial sooner and receive income from the drug for longer until the patent expires, or drip-feeding investment slowly and analysing initial results to make more informed decisions. Thus, the simple gain functions used widely in Chapters 3 and 4 are not sufficient. Therefore, as introduced in Section 1.5.1, we define a gain function motivated by the financial model gain functions in Parke et al. (2017) and Patel et al. (2012) which aim to model the net present value (NPV) of a programme.

We define the gain function $\mathcal{G}(\mathfrak{I}_3, \theta)$ as

$$\mathcal{G}(\mathfrak{I}_3, \theta) := \text{Discounted Net Revenue} - \text{Phase II Cost} - \text{Phase III Cost}. \tag{5.1}$$

If H_0 is rejected, there is an income at $t > T_{\text{PhII}} + T_{\text{PhIII}}$, which are defined by

$$\begin{aligned} T_{\text{PhII}} :=& T_{\text{PhII setup}} + T_{\text{PhII pat}} n_1 \\ T_{\text{PhIII}} :=& T_{\text{PhIII setup}} + T_{\text{PhIII pat}} n_2. \end{aligned} \tag{5.2}$$

We model the revenue per year as constant when the patent is in force, with an exponential decay once the patent runs out, modelling the emergence of generic brand competitors that will arise once the patent expires as

$$G(t, T_{\text{pat}}) := \begin{cases} G_{\text{rev}} & \text{if } t < T_{\text{pat}} \\ G_{\text{rev}} e^{-c(t - T_{\text{pat}})} & \text{if } t \geq T_{\text{pat}}. \end{cases} \tag{5.3}$$

Then we may define

$$\text{Discounted Net Revenue} := \mathbb{1}_{(H_0 \text{ rejected})} \times \int_{T_{\text{PhII}} + T_{\text{PhIII}}}^{\infty} G(t, T_{\text{pat}}) e^{-\rho t} dt, \tag{5.4}$$

and

$$\begin{aligned} \text{Phase II Cost} :=& \gamma_1 2 n_1 + \gamma_{\text{Ph II overhead}} \\ \text{Phase III Cost} :=& (\gamma_2 2 n_2 + \gamma_{\text{PhIII overhead}}) e^{-\rho T_{\text{PhII}}} \end{aligned} \tag{5.5}$$

The expression for the discounted net revenue can be expressed as

$$\begin{aligned} &\text{Discounted Net Revenue} \\ =& \mathbb{1}_{(H_0 \text{ rejected})} \times \int_{T_{\text{PhII}} + T_{\text{PhIII}}}^{\infty} G(t, T_{\text{pat}}) e^{-\rho t} dt \\ =& \mathbb{1}_{(H_0 \text{ rejected})} \times \left(\int_{T_{\text{PhII}} + T_{\text{PhIII}}}^{T_{\text{pat}}} G_{\text{rev}} e^{-\rho t} dt + \int_{T_{\text{pat}}}^{\infty} G_{\text{rev}} e^{-(\rho + c)t + c T_{\text{pat}}} dt \right) \\ =& \mathbb{1}_{(H_0 \text{ rejected})} \times \left(\frac{G_{\text{rev}}}{\rho} (e^{-\rho(T_{\text{PhII}} + T_{\text{PhIII}})} - e^{-\rho T_{\text{pat}}}) + \frac{G_{\text{rev}}}{c + \rho} e^{-\rho T_{\text{pat}}} \right). \end{aligned} \tag{5.6}$$

5.1.3 Examples

In this chapter, we explore the answers to different questions relating to how best to perform Phase III when we require two Phase III trials. Initially we concern ourselves with the problem of whether to perform both trials in parallel, or attempt to learn from one trial before committing resources to a second. After that, we investigate whether a compromise between the two approaches may be appropriate in some scenarios. Lastly we consider the case when the two Phase III trials have group sequential designs.

Similarly to Chapters 3 and 4, we take the approach of optimising each individual programme by finding the optimal decision rules at each decision point with respect to the gain function. The programmes may then be compared to each other to assess the benefit of the different

approach each programmes take. In contrast to these chapters, we compute decision rules only using numerical integration without resorting to Monte Carlo simulation methods.

5.2 Studies to assess how best to perform two Phase IIIs

5.2.1 Programmes 1 and 2

Given that Phase III consists of two trials, one may ask when they should be performed. In particular, should they be performed sequentially (one after the other) or in parallel (at the same time). The answer to this question will depend upon the parameters specified within the gain function, and any prior knowledge about the drug itself.

In particular, the decision may come down to a trade off between starting both Phase IIIs early in the hope of finishing as quickly as possible, or starting only Phase IIIa, in the hope of learning more before committing to Phase IIIb.

In this section, we define Programmes 1 and 2, and consider computational techniques to evaluate the optimal decision rules within the programme.

We suppose there is a single treatment to be considered at the start of the programme and the primary response is normally distributed with known variance σ^2, and means $\mu^{(t)}$ and $\mu^{(c)}$ for treatment and control. Define $\theta := \mu^{(t)} - \mu^{(c)}$ as the treatment effect vector. A high treatment effect will indicate a successful treatment compared to control. We assume that primary responses are observed in both Phase II and III. We define the one-sided null hypotheses $H: \ \theta \leq 0$ for each Phase III trial.

The programmes have multiple decision points in which decisions regarding the sample size related to the next phase will be made. Data that has been accumulated prior to each decision point may be used to inform the decision. Each Phase III trial uses data from that trial only, and the hypothesis test must result in a rejection of the null hypothesis when applied to both Phase III trials separately for the programme to be successful and the marketing revenues realised. We suppose also that all trials are fixed sample and call the two Phase III trials Phase IIIa and Phase IIIb.

Programme 1: Phase III trials in parallel

Background

Programme 1 concerns the case when Phase IIIa and IIIb are performed in parallel. That is, after Phase II has concluded, both Phase IIIa and IIIb are started at the same time.

This programme may be advantageous when there is a rush to gain regulatory approval and get the treatment to market sooner. This may be appropriate when the patients are relatively inexpensive to treat, the potential revenue is large, or when the current belief about the treatment effect is that it has high efficacy. We suppose the sample size for Phase IIIb is the same as for Phase IIIa, $n_3 = n_2$.

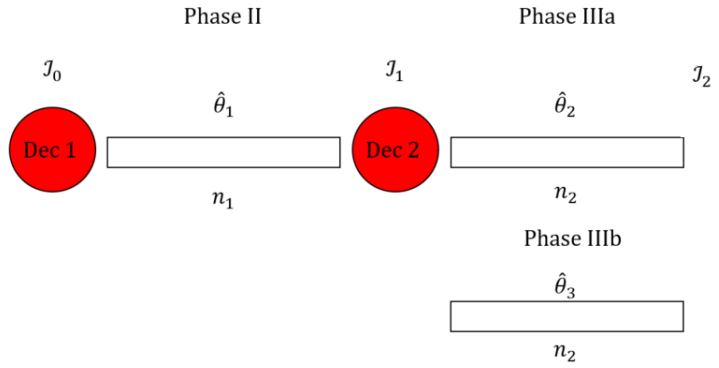

Figure 5-1: Programme 1 schematic.

As shown in Figure 5-1, there are two decision points which we call Decision 1 and Decision 2.

Computing the optimal decision rules

Below we define notation for the optimal decisions in Decision 1 and 2, and derive the optimal decisions and discuss their computations. Firstly, we must define the cumulative summary statistic,

$\mathfrak{I}_2 := (\mathfrak{I}_1, \hat{\theta}_2, \hat{\theta}_3)$, the set of cumulative summary statistics formed from $\mathfrak{I}_1$ plus summary statistics from Phase IIIa and IIIb.

Let $\mathcal{D}_i(\mathfrak{I}_{i-1})$ be the optimal decision i, for $i = 1, 2$, given the information in $\mathfrak{I}_{i-1}$.

Let $\mathfrak{G}_i(n_i, \mathfrak{I}_{i-1})$, $i = 1, 2, 3$, be the expected gain given $\mathfrak{I}_{i-1}$ and a choice of sample size n_i for Phase i, and assuming optimal decisions are made in future decision points.

We suppose the prior for the treatment effect θ is distributed according to $N(\theta_0, \Sigma_0)$. At Decision 1, the sampling distribution of $\hat{\theta}_1$, denoted $\pi(\hat{\theta}_1; \mathfrak{I}_0, n_1)$ may be found as follows. For a fixed sample design, the conditional (on θ) distribution of summary statistic is $\hat{\theta}_1 \sim N(\theta, 2\sigma^2/n_1)$. By considering the moment generating function of the marginal distribution of $\hat{\theta}_1$, we find

$$\hat{\theta}_1 \sim N(\theta_0, 2\sigma^2/n_1 + \Sigma_0). \tag{5.7}$$

Similarly for Decision 2, suppose the posterior distribution of θ given $\mathfrak{I}_1$ is $\theta \sim N(\varphi, \nu^2)$ with probability density function $\pi(\theta; \mathfrak{I}_1)$ where φ and ν can be deduced from $\mathfrak{I}_1$. The sampling distribution $\hat{\theta}_2$, denoted $\pi(\hat{\theta}_2; \mathfrak{I}_1, n_2)$ is

$$\hat{\theta}_2 \sim N(\varphi, 2\sigma^2/n_2 + \nu^2). \tag{5.8}$$

Decision 2:

$$\mathcal{D}_2(\mathfrak{I}_1) = \underset{n_2}{\operatorname{argmax}}\, \mathfrak{G}_2(n_2, \mathfrak{I}_1) \tag{5.9}$$

In order to compute this, we integrate over the treatment effect θ, weighted by its posterior distribution given $\mathfrak{I}_1$, $\pi(\theta; \mathfrak{I}_1)$.

$$\begin{aligned} \mathcal{D}_2(\mathfrak{I}_1) &= \underset{n_2}{\operatorname{argmax}}\ \mathfrak{G}_2(n_2, \mathfrak{I}_1) \\ &= \underset{n_2}{\operatorname{argmax}} \int_\theta \mathbb{E}[\mathcal{G}(\mathfrak{I}_2) \mid \mathfrak{I}_1, n_2, \theta]\ \pi(\theta; \mathfrak{I}_1)\ d\theta \end{aligned} \tag{5.10}$$

The expectation in Equation 5.10 can be easily computed. Each evaluation of the integrand simply requires calculating the probability of rejection of the null hypothesis in both Phase III trials given θ. Therefore the integral in its general form may be computed using the numerical integration methods described in Section 1.6.1.

Decision 1:

We integrate over the maximum likelihood estimate of θ, $\hat{\theta}_1$, with sampling distribution density function given $\mathfrak{I}_0$, $\pi(\hat{\theta}_1; \mathfrak{I}_0, n_1)$.

$$\begin{aligned}
\mathcal{D}_1(\mathfrak{I}_0) &= \underset{n_1}{\text{argmax}} \ \mathfrak{G}_1(n_1, \mathfrak{I}_0) \\
&= \underset{n_1}{\text{argmax}} \ \int_{\hat{\theta}_1} \mathbb{E}[\mathcal{G}(\mathfrak{I}_2) \mid \mathfrak{I}_0, n_1, \hat{\theta}_1] \ \pi(\hat{\theta}_1; \mathfrak{I}_0, n_1) \ d\hat{\theta}_1 \\
&= \underset{n_1}{\text{argmax}} \ \int_{\hat{\theta}_1} \mathbb{E}[\mathcal{G}(\mathfrak{I}_2) \mid \mathfrak{I}_1] \ \pi(\hat{\theta}_1; \mathfrak{I}_0, n_1) \ d\hat{\theta}_1
\end{aligned} \tag{5.11}$$

Note that n_2 is chosen according to Decision 2 such that

$$\mathbb{E}[\mathcal{G}(\mathfrak{I}_1) \mid \mathfrak{I}_1] = \mathfrak{G}_2(\mathcal{D}_2(\mathfrak{I}_1), \mathfrak{I}_1). \tag{5.12}$$

Therefore, we have

$$\begin{aligned}
\mathcal{D}_1(\mathfrak{I}_0) &= \underset{n_1}{\text{argmax}} \ \mathfrak{G}_1(n_1, \mathfrak{I}_0) \\
&= \underset{n_1}{\text{argmax}} \ \int_{\hat{\theta}_1} \mathfrak{G}_2(\mathcal{D}_2(\mathfrak{I}_1), \mathfrak{I}_1) \ \pi(\hat{\theta}_1; \mathfrak{I}_0, n_1) \ d\hat{\theta}_1
\end{aligned} \tag{5.13}$$

As in Decision 1, the numerical integration techniques in Section 1.6.1 may be used to solve this integral. No Monte Carlo simulation based approaches are necessary. An evaluation of $\mathcal{D}_1(\mathfrak{I}_0)$ requires computing $\mathfrak{G}_2(\mathcal{D}_2(\mathfrak{I}_1), \mathfrak{I}_1)$ for different $\hat{\theta}_1$, so Decision 1 is more computationally intensive than Decision 2.

One may reduce the computational expense required to compute $\mathcal{D}_1(\mathfrak{I}_0)$ for different n_1 by storing the value of $\mathfrak{G}_2(\mathcal{D}_2(\mathfrak{I}_1), \mathfrak{I}_1)$ for a grid of different values of $\hat{\theta}_1$, and using these grid points in the integration routine for each evaluation of $\mathcal{D}_1(\mathfrak{I}_0)$. This is the method of dynamic programming.

Programme 2: Phase III trials in sequence

Background

Programme 2 concerns the case when Phase IIIa and IIIb are performed sequentially. That is, after Phase II has concluded, Phase IIIa commences, and Phase IIIb commences after Phase IIIa has finished.

This programme may be advantageous when there is no particular rush to gain regulatory approval and get the treatment to market sooner. This may be appropriate when the patients are more expensive to treat, the potential revenue is relatively small, or when the current belief about the treatment effect is uncertain and one wants to proceed cautiously. We introduce the cumulative summary statistics,

$\mathfrak{I}_2 := (\mathfrak{I}_1, \hat{\theta}_2)$, the set of cumulative summary statistics formed from $\mathfrak{I}_1$ plus summary

statistics from Phase IIIa.

$\mathfrak{I}_3 := (\mathfrak{I}_1, \hat{\theta}_3)$, the set of cumulative summary statistics formed from $\mathfrak{I}_2$ plus summary statistics from Phase IIIb.

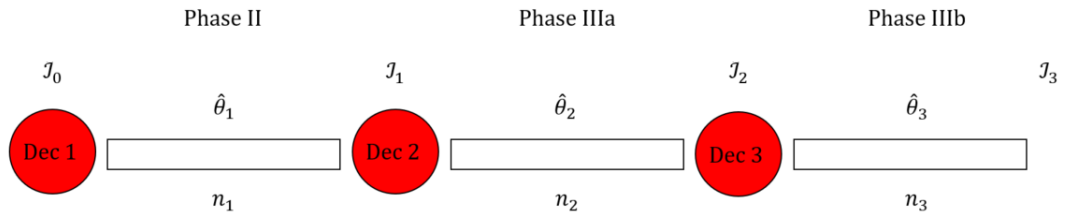

Figure 5-2: Programme 2 schematic.

As shown in Figure 5-2, there are three decision points at Decision 1, Decision 2, and Decision 3.

Computing the optimal decision rules

Decision 3:

As in Decision 2 in Programme 1, we get

$$\begin{aligned} \mathcal{D}_3(\mathfrak{I}_2) &= \underset{n_3}{\text{argmax}} \;\; \mathfrak{G}_3(n_3, \mathfrak{I}_2) \\ &= \underset{n_3}{\text{argmax}} \;\; \int_\theta \mathbb{E}[\mathcal{G}(\mathfrak{I}_3) \mid \mathfrak{I}_2, n_3, \theta] \; \pi(\theta; \mathfrak{I}_2) \; d\theta. \end{aligned} \tag{5.14}$$

Decision 2:

As in Decision 1 in Programme 1, we have

$$\begin{aligned} \mathcal{D}_2(\mathfrak{I}_1) &= \underset{n_2}{\text{argmax}} \;\; \mathfrak{G}_2(n_2, \mathfrak{I}_1) \\ &= \underset{n_2}{\text{argmax}} \;\; \int_{\hat{\theta}_2} \mathfrak{G}_3(\mathcal{D}_3(\mathfrak{I}_2), \mathfrak{I}_2) \; \pi(\hat{\theta}_2; \mathfrak{I}_1, n_2) \; d\hat{\theta}_2. \end{aligned} \tag{5.15}$$

Decision 1:

In the same way as Decision 2 above, we find

$$\begin{aligned} \mathcal{D}_1(\mathfrak{I}_0) &= \underset{n_1}{\text{argmax}} \;\; \mathfrak{G}_1(n_1, \mathfrak{I}_0) \\ &= \underset{n_1}{\text{argmax}} \;\; \int_{\hat{\theta}_1} \mathfrak{G}_2(\mathcal{D}_2(\mathfrak{I}_1), \mathfrak{I}_1) \; \pi(\hat{\theta}_1; \mathfrak{I}_0, n_1) \; d\hat{\theta}_1. \end{aligned} \tag{5.16}$$

As before, each decision can be calculated using numerical integration techniques with no simulation required, with Decision 1 most intensive and Decision 3 the least intensive. The method of dynamic programming can as before be used.

5.2.2 Programme Comparison A: Comparison of Programmes 1 and 2

We compare and contrast Programmes 1 and 2 in a variety of settings. Unless otherwise stated, we use the following parameters for this study:

Table 5.1: Programme Comparison A Parameters

$\sigma =$	3	$T_{\text{PhII setup}} =$	0.1	$T_{\text{PhII overhead}} =$	500
$\alpha =$	0.025	$T_{\text{PhIII setup}} =$	0.1	$T_{\text{PhIII overhead}} =$	200
$G_{\text{rev}} =$	5000	$T_{\text{PhII pat}} =$	0.005	$c =$	5
$T_{\text{patent}} =$	15	$T_{\text{PhIII pat}} =$	0.005	$N_1, N_2, N_3 =$	(0,25,50,75,...)
$\rho =$	0.03	$\gamma_1, \gamma_2 =$	(1,1)	$\zeta =$	Identity function

In the following subsections, we look at the differences between the two programmes, and consider which is the best programme under different circumstances.

5.2.3 A comparison of Programmes 1 and 2 at Decision 1

Suppose that the prior distribution parameters are $\mu_0 = 0$ and $\Sigma_0 = 1$, such that $\theta \sim N(0, 1)$. Then the optimal decision about Decision 1 and corresponding expected gain of the entire programme for Programmes 1 and 2 are given in the below table.

	Programme 1	Programme 2
Optimal n_1	50	0
Corresponding expected gain	13,386	11,884

Programme 1 has a higher expected gain compared to Programme 2 for this set of parameters and prior distribution. Programme 2 in particular has an optimal decision of not performing Phase II ($n_1 = 0$) and proceeding straight to Phase IIIa with a sample size of 275 patients per arm. The information from Phase IIIa is adequate to inform the sample size of Phase IIIb, without the need to use up time performing Phase II which reduces the time left until the patent expires. In Programme 1, this is less of an issue, as the two Phase III trials are performed at the same time. This means however, a small Phase II trial of 50 patients per arm is justified in order to inform the sample size of the two Phase III trials.

Optimal decision rules in Decision 2

Using the decision rules in Equations 5.10 and 5.15, one may calculate the optimal decision rules for each programme.

As an example, suppose that after Phase II with $n_1 = 100$, we have the posterior belief that the true treatment effect follows $\theta \sim N(\mu, 1)$. In this section, we examine the optimal decision rules in Decision 1 for the choice of n_2 as the value of μ varies. Note that $n_2 = 0$ means no further trials are performed.

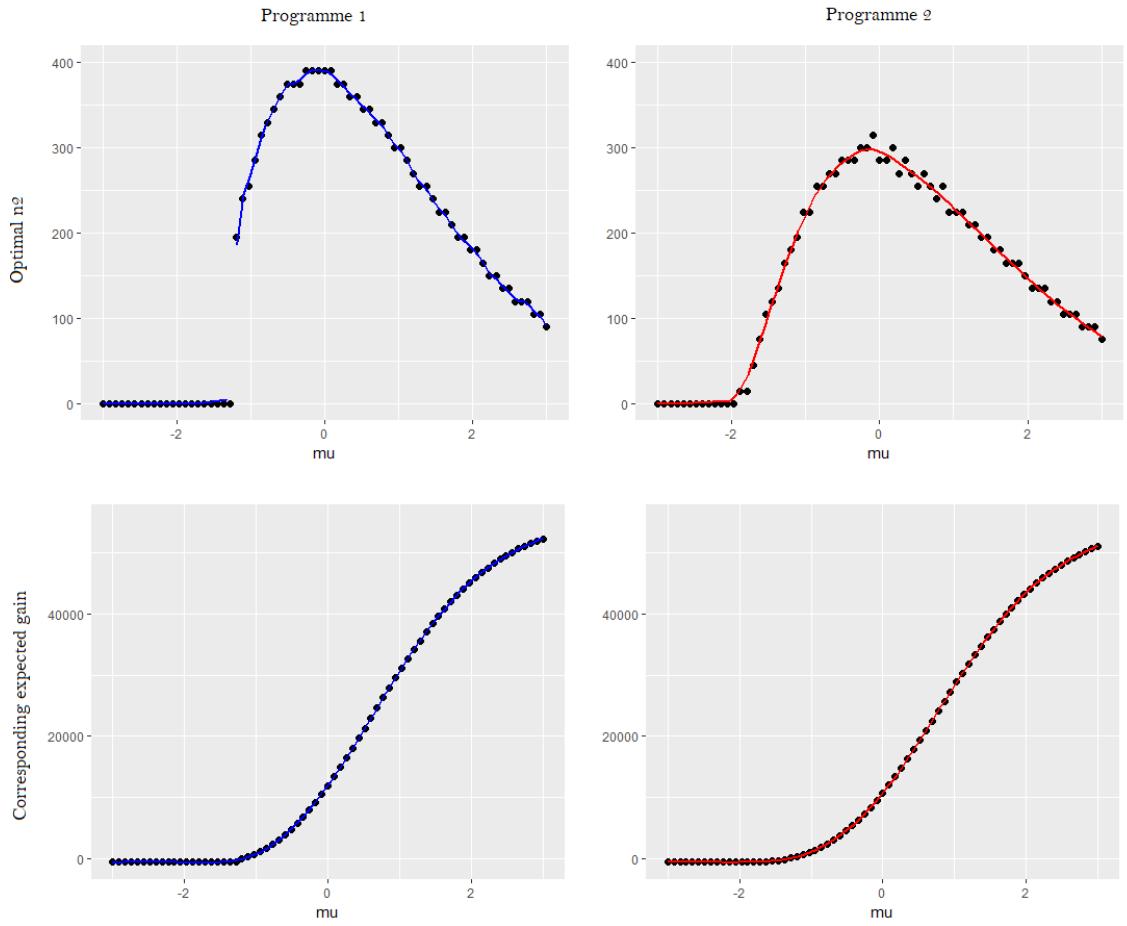

Figure 5-3: Optimal decision curves for Decision 2 as functions of the mean of the posterior distribution μ. The top row is the optimal choice of n_2 given each value of μ, with the corresponding expected gain given in the bottom row. The first and second columns refer to Programmes 1 and 2 respectively.

From Figure 5-3, it is particularly apparent in Programme 2 that there are only marginal differences between the expected gain corresponding to some values of n_2 when there is flexibility to make further decisions later on in the programme. In these cases, the choice of the optimal n_2 becomes sensitive to numerical error from the numerical integration, so the optimal n_2 values do not follow a smooth curve as μ increases. The numerical error one obtains may be larger than one would have expected. Due to the discontinuous values N_2,N_3 can take, the integrand is not smooth in its first derivative, meaning the numerical integration technique based on Simpsons' rule may perform badly near these discontinuities in the first derivative. However, given that the corresponding expected gains are very similar for a range of different n_2 in these cases, this is not a serious problem.

The best programme at Decision 2

Again, suppose Phase II is performed with $n_1^{(t)} = 100$ for both treatment and control and after it has completed, we suppose the current belief in the treatment effect is that $\theta \sim N(\mu, 1)$. We assume $\mu = 0$ unless otherwise specified.

In the following comparisons, we vary the cost of treating Phase II, IIIa, and IIIb patients, and the time to treat each patient. For each combination, we identify which programme has a higher expected gain.

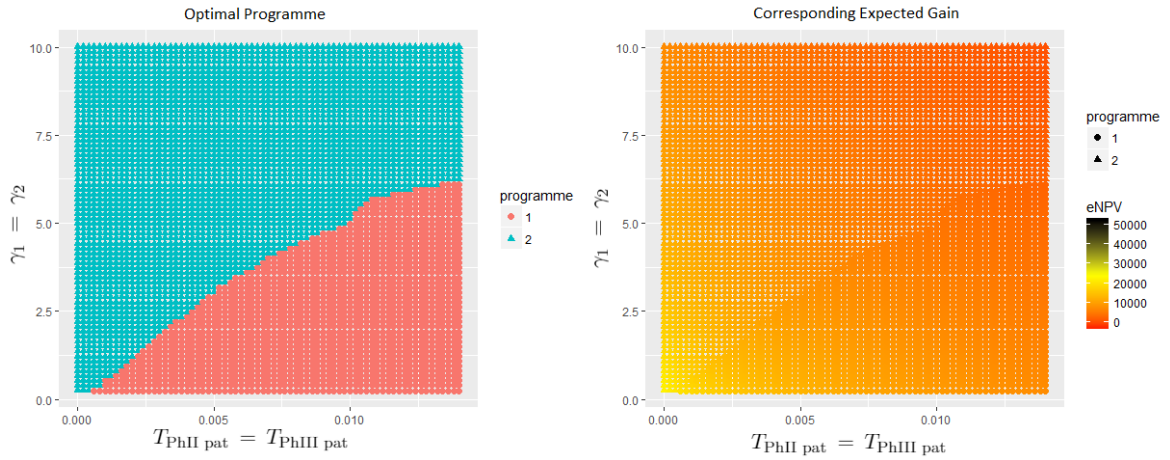

Figure 5-4: Left: The optimal programme as $\gamma_1 = \gamma_2$ (denoted by `gamma`) and $T_{\text{PhII pat}} = T_{\text{PhIII pat}}$ are varied. Right: The corresponding expected gain of the optimal programme for each pair of $\gamma_1 = \gamma_2$ and $T_{\text{PhII pat}} = T_{\text{PhIII pat}}$.

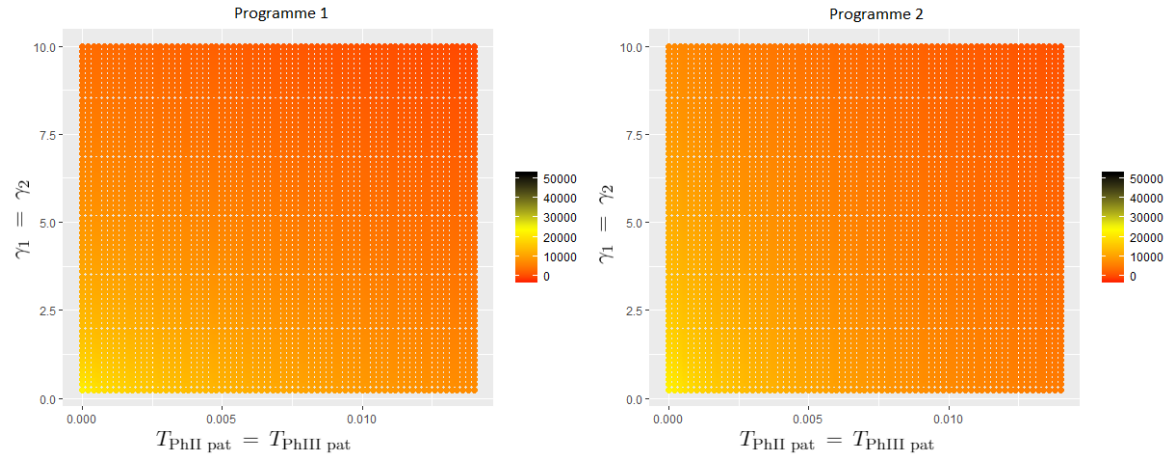

Figure 5-5: The expected gain for each programme corresponding to Figure 5-4.

We now repeat the above analysis for Figures 5-4 and 5-5 for when some assumptions are changed. In particular when the parameter μ is reduced, representing a more pessimistic belief in the efficacy of the treatment, and when G_{rev} in the defintion of $G(t, T_{\text{pat}})$ is doubled, representing larger revenues for this particular treatment.

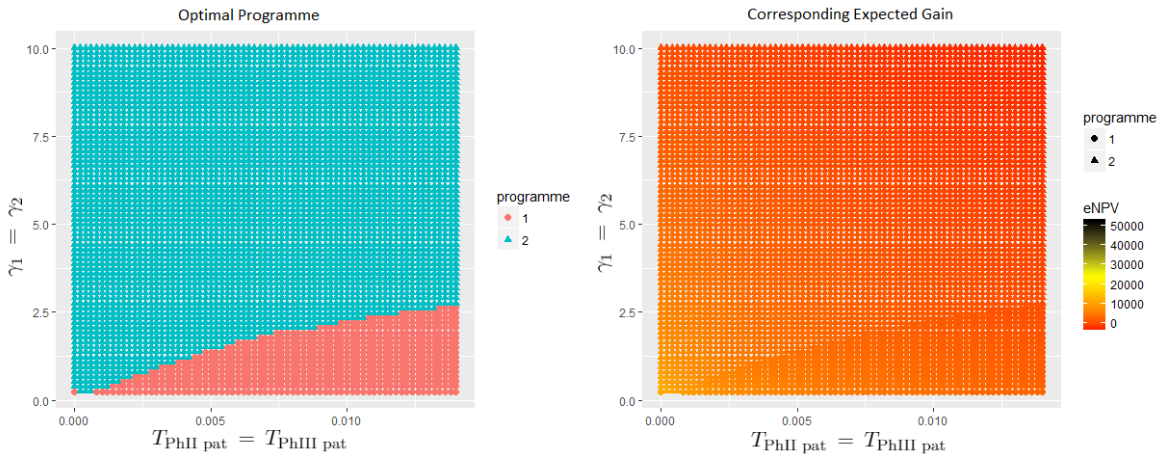

Figure 5-6: As in Figure 5-4, but with $\vartheta = -0.5$.

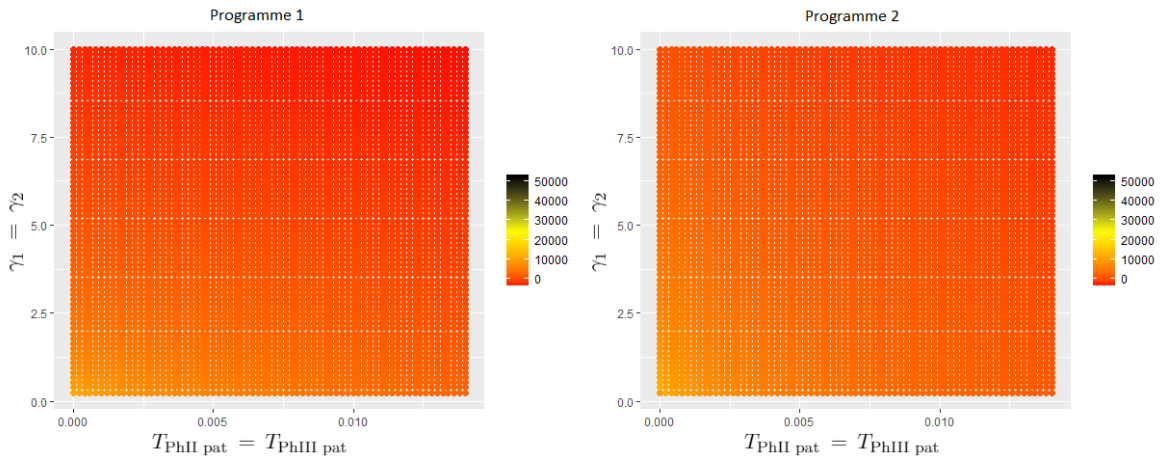

Figure 5-7: The expected gain for each programme corresponding to Figure 5-6.

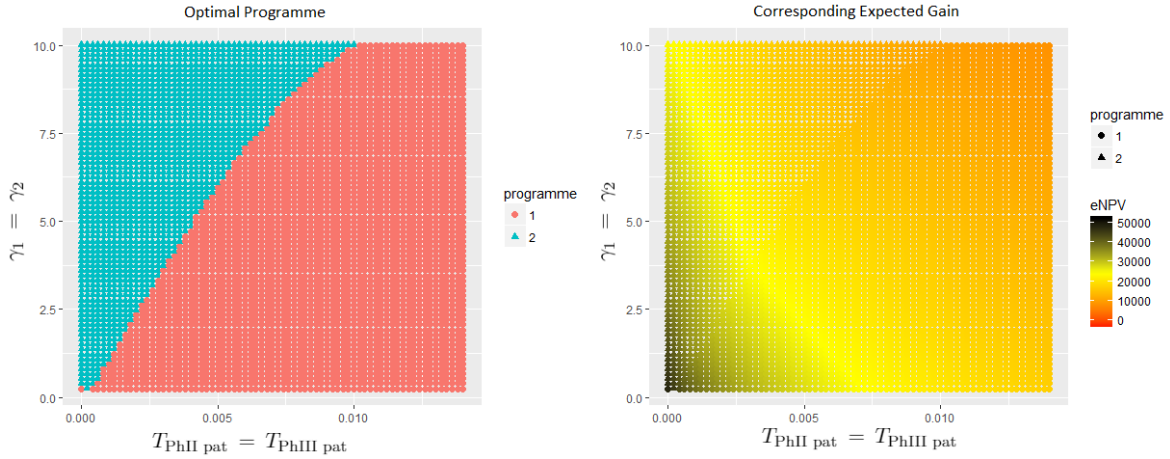

Figure 5-8: As in Figure 5-4, but with $G_{\text{rev}} = 10000$.

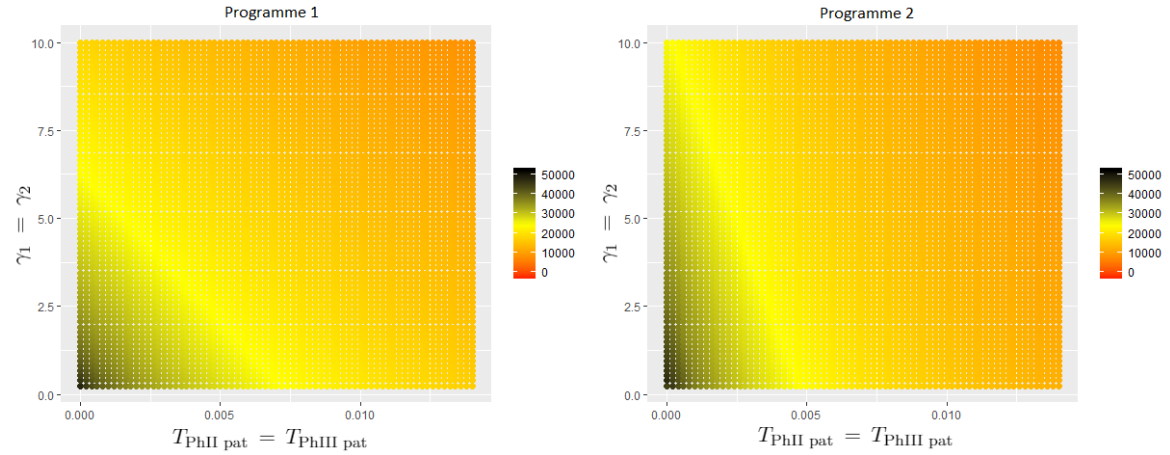

Figure 5-9: The expected gain for each programme corresponding to Figure 5-8.

From Figures 5-6 to 5-9, one may deduce the best programme design to use depends significantly upon the parameters. Higher values for patient cost lead to favouring a sequential design over parallel, as do lower values of the time taken to test a patient. A more pessimistic outlook about the treatment effect of the drug favours a sequential design, and a larger potential benefit from finding the drug works favours a parallel design.

5.2.4 Programme 3: Adding in adaptation

Motivation

In the programme comparison study in Section 5.2.2, it was found there was a trade off between starting both Phase IIIa and PhIIIb in parallel in order to minimise time until regulatory approval versus starting only Phase IIIa in order to gain more information to make more informed decisions about Phase IIIb. One might ask if there is a middle ground,

where Phase IIIb could be started halfway through Phase IIIa at that point if the results so far give evidence to support this action.

Motivated by this, we define Programme 3 which follows the pattern of Programme 2 until halfway through Phase IIIa. At this point, an interim analysis occurs, and a decision is made whether to stop the programme, start Phase IIIb immediately, or to delay the decision by continuing to the end of Phase IIIa and then consider whether to start Phase IIIb.

Clearly, an optimal version of this programme should dominate Programme 2 as it allows one to proceed according to Programme 2, whilst allowing the freedom to deviate from Programme 2 if it is beneficial. That is, Programme 2 is a special case of Programme 3.

In this programme, we must modify existing notation and introduce new notation.

$\hat{\theta}_2'$, the maximum likelihood estimate of θ from data from the first half of Phase IIIa.

$\hat{\theta}_2''$, the maximum likelihood estimate of θ from data from the second half (only) of Phase IIIa.

$\mathfrak{I}_2 := (\mathfrak{I}_1, \hat{\theta}_2')$, the set of cumulative summary statistics formed from $\mathfrak{I}_1$ plus summary statistics from the first half of Phase IIIa.

$\mathfrak{I}_3 := (\mathfrak{I}_2, \hat{\theta}_2'')$, the set of cumulative summary statistics formed from $\mathfrak{I}_2$ plus summary statistics from the second half of Phase IIIa.

$\mathfrak{I}_4 := (\mathfrak{I}_1, \hat{\theta}_3)$, the set of cumulative summary statistics formed from $\mathfrak{I}_3$ plus summary statistics from Phase IIIb.

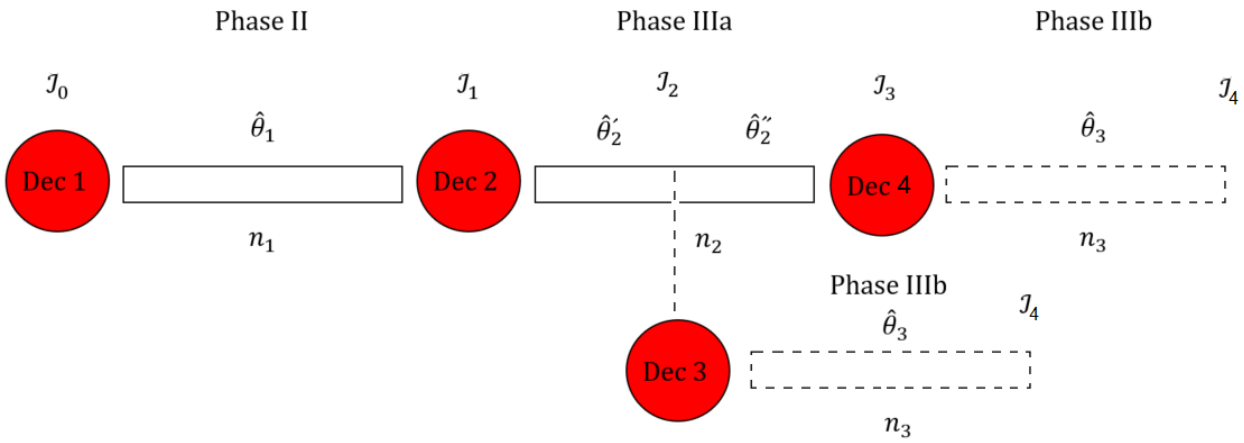

Figure 5-10: Programme 3 schematic.

Administrative Considerations

We note that a protocol which involves an interim analysis halfway through Phase IIIa and performing an action based upon the data observed may be viewed as unacceptable. Consider the case where based upon the interim analysis, a decision is made to start Phase IIIb with a small sample size. From this, one might infer that the treatment has performed well in the first part of the Phase IIIa trial, so there is information leakage to those who understand the rules of the trial design and learn about the choice of sample size for the Phase IIIb trial. This goes against the principle of maintaining blindness of the results of a trial until its completion. We shall investigate this programme design anyway to identify the possible benefits the approach could bring.

Computational approaches

As before, we derive the analytical expressions for the optimal decision rules at each decision point for Programme 3.

Decision 4:

As in Decision 3 in Programme 2, we get

$$\begin{aligned}\mathcal{D}_4(\mathfrak{I}_3) &= \underset{n_3}{\text{argmax}}\ \mathfrak{G}_4(n_3, \mathfrak{I}_3) \\ &= \underset{n_3}{\text{argmax}}\ \int_\theta \mathbb{E}[\mathcal{G}(\mathfrak{I}_4) \mid \mathfrak{I}_3, n_3, \theta]\pi(\theta; \mathfrak{I}_3)d\theta\end{aligned} \tag{5.17}$$

Decision 3:

In Decision 3, we have the choice of either

- Waiting until Decision 4,
- Terminate the entire trial, or
- Starting Phase IIIb with a specified n_3.

$$\begin{aligned}\mathcal{D}_3(\mathfrak{I}_2) &= \underset{\text{action} \in \{\text{wait,stop,start phIIIb}\}}{\text{argmax}}\ \mathfrak{G}_3(\mathfrak{I}_2, \text{action}), \\ \text{where}\ \ \mathfrak{G}_3(\mathfrak{I}_2; \text{start phIIIb}) &= \max_{n_3} \int_\theta \mathbb{E}[\mathcal{G}(\mathfrak{I}_4)|\mathfrak{I}_2, n_3, \theta]\pi(\theta; \mathfrak{I}_2)d\theta,\end{aligned} \tag{5.18}$$

$$\begin{aligned}\mathfrak{G}_3(\mathfrak{I}_2; \text{wait}) &= \int_{\hat{\theta}_2''} \mathbb{E}[\mathcal{G}(\mathfrak{I}_3)|\mathfrak{I}_2, n_2, \hat{\theta}_2'']\pi(\hat{\theta}_2''; \mathfrak{I}_2, n_2)d\hat{\theta}_2'' \\ &= \int_{\hat{\theta}_2''} \mathfrak{G}_4(\mathcal{D}_4(\mathfrak{I}_3), \mathfrak{I}_3)\pi(\hat{\theta}_2''; \mathfrak{I}_2, n_2)d\hat{\theta}_2'',\ \text{and}\end{aligned} \tag{5.19}$$

$$\mathfrak{G}_3(n_3, \mathfrak{I}_2; \text{stop}) = -2\gamma_1 n_1 - \gamma_{\text{PhII overhead}} - (\gamma_2 \frac{2n_2}{2} + \gamma_{\text{PhIII overhead}})e^{-\rho T_{\text{PhII}}}.$$

Decision 2:

$$\begin{aligned}\mathcal{D}_2(\mathfrak{I}_1) &= \underset{n_2}{\text{argmax}}\ \mathfrak{G}_2(n_2, \mathfrak{I}_1) \\ &= \underset{n_2}{\text{argmax}}\ \int_{\hat{\theta}_2'} \mathfrak{G}_3(\mathcal{D}_3(\mathfrak{I}_2), \mathfrak{I}_2)\pi(\hat{\theta}_2'; \mathfrak{I}_1, n_2)d\hat{\theta}_2'\end{aligned} \tag{5.20}$$

Decision 1:

$$\begin{aligned}\mathcal{D}_1(\mathfrak{I}_0) &= \underset{n_1}{\text{argmax}}\ \mathfrak{G}_1(n_1, \mathfrak{I}_0) \\ &= \underset{n_1}{\text{argmax}}\ \int_{\hat{\theta}_1} \mathfrak{G}_2(\mathcal{D}_2(\mathfrak{I}_1), \mathfrak{I}_1)\pi(\hat{\theta}_1; \mathfrak{I}_0, n_1)d\hat{\theta}_1\end{aligned} \tag{5.21}$$

As before, we use numerical integration routines to calculate the optimal designs. No Monte Carlo based simulation methods are requried.

5.2.5 Programme Comparison B: The value of adaptivity

Comparing Programmes 1,2, and 3

We compare the performance of Programme 3 relative to the other programmes using the same input parameters as in Section 5.2.3.

	Programme 1	Programme 2	Programme 3
Optimal n_1	50	0	0
Corresponding expected gain	13,386	11,884	13,067

The adaptations in Programme 3 add value to the programme compared to having no adaptations in Programme 2. The optimal decisions with these parameters recommend proceeding straight to Phase III as was the case for Programme 2. However, the programme is still inferior to performing the Phase III trials in parallel as in Programme 1 under these parameters.

Optimal decisions in Decision 2 for each programme

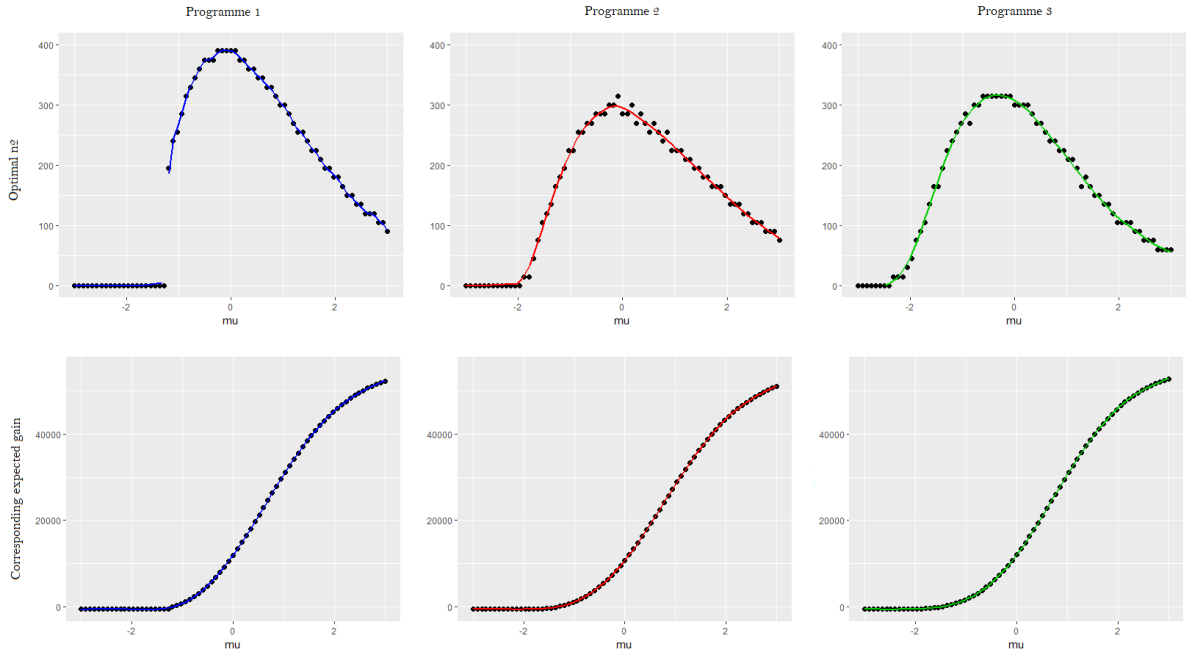

Figure 5-11: As in Figure 5-3, optimal decision curves for Decision 2 as functions of the mean of the posterior distribution μ. The top row is the optimal choice of n_2 given each value of μ, with the corresponding expected gain given in the bottom row. The columns refer to Programmes 1, 2, and 3 respectively.

The best programme at Decision 2

As in Programme Comparison A, we compare the decisions the programmes make in Decision 2 as the cost of testing a patient γ and the time to test a patient T_{pat} vary. Since Programme 2 is dominated by Programme 3, we only consider Programmes 1 and 3.

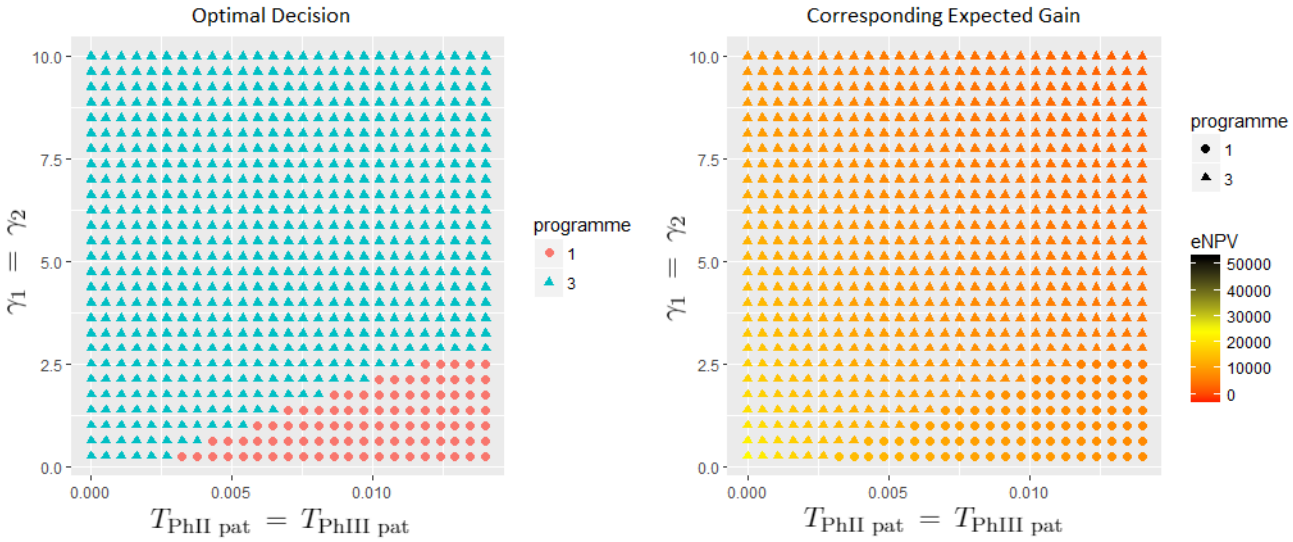

Figure 5-12: The optimal programme and corresponding expected gain when $\theta \sim N(0, 1)$ with $G = 5000$.

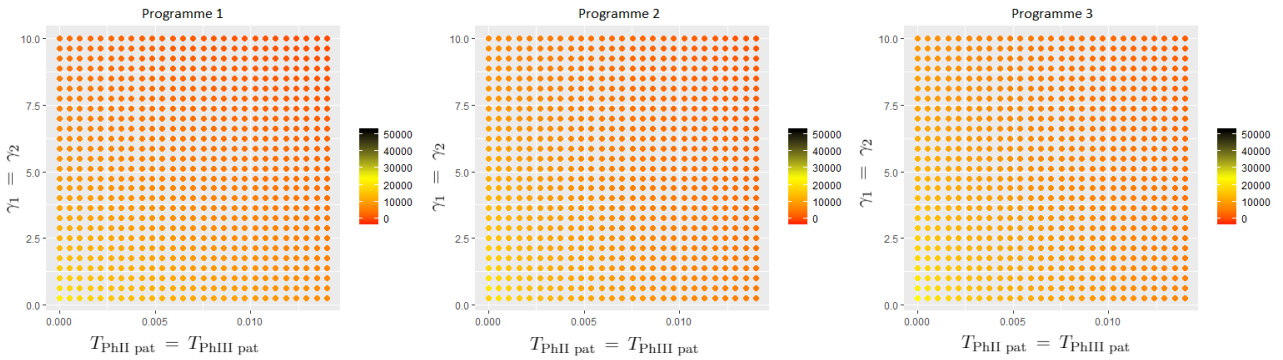

Figure 5-13: The expected gain of each programme corresponding to Figure 5-12.

We then repeat this analysis as the posterior distribution of θ, and the revenue G change.

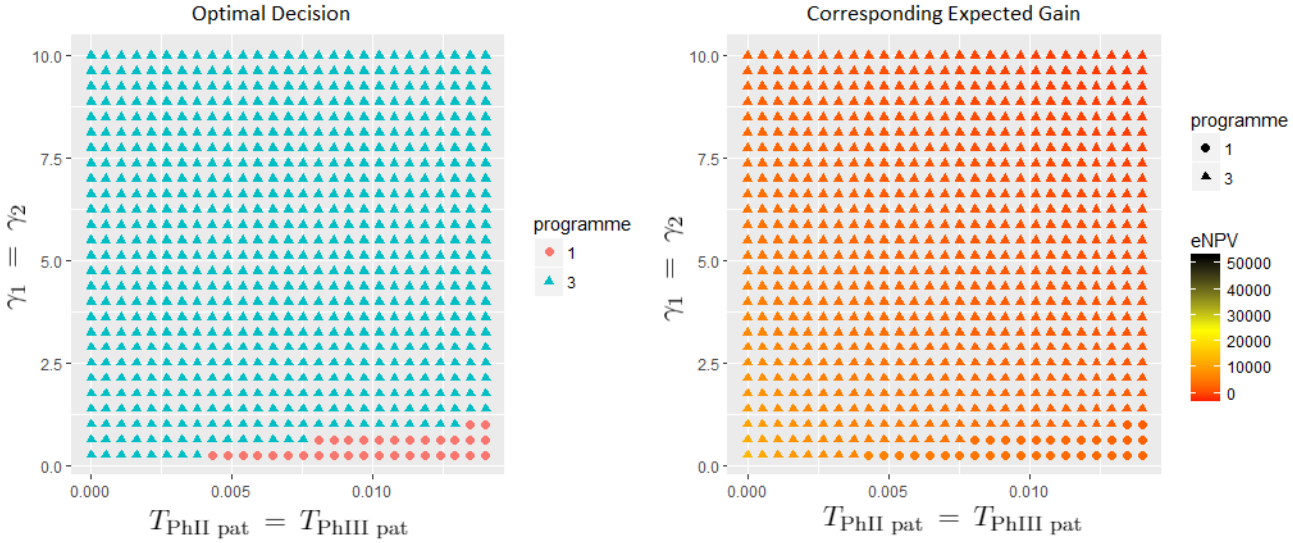

Figure 5-14: The optimal programme and corresponding expected gain when $\theta \sim N(-0.5, 1)$ with $G = 5000$.

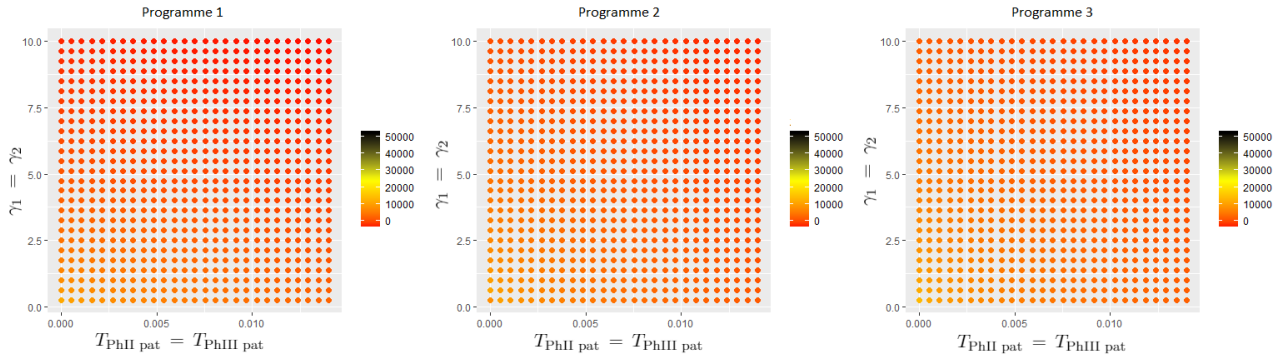

Figure 5-15: The expected gain of each programme corresponding to Figure 5-14.

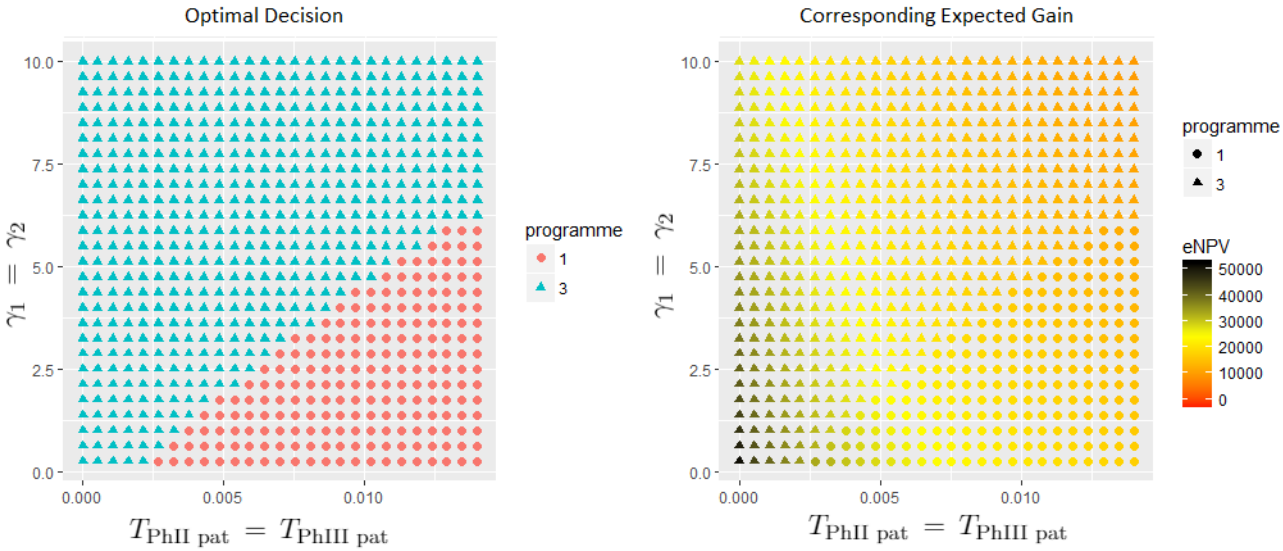

Figure 5-16: The optimal programme and corresponding expected gain when $\theta \sim N(0, 1)$ with $G = 10000$.

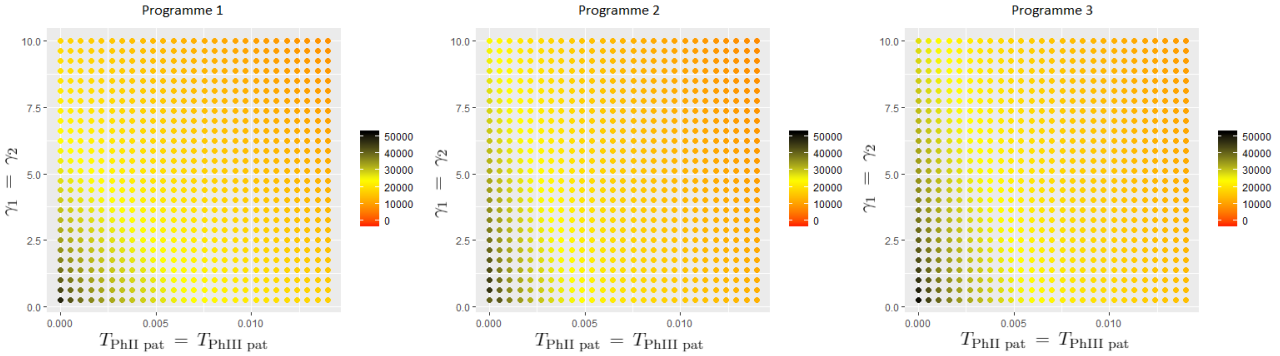

Figure 5-17: The expected gain of each programme corresponding to Figure 5-16.

Comparing Figures 5-12, 5-14, 5-16 to Figures 5-4, 5-6, 5-8, we see that Programme 1 is optimal in less of the T_{pat} and γ sample space. That is in some circumstances, introducing adaptation in the form of Programme 3 means it becomes advantageous to start Phase III sequentially with the option to adapt halfway through the first Phase III trial rather than in parallel, which would be preferred if there is no adaptation.

Comparing Figures 5-12, 5-14, 5-16, one can see as before that if one is more pessimistic about the true treatment effect, in more cases it is advantageous to have Phase III sequentially in the form of Programme 3. On the other hand if the revenue is expected to be larger from a successful drug, in more cases it is advantageous to have the Phase III trials in parallel as in Programme 1.

Optimal decisions in Decision 3

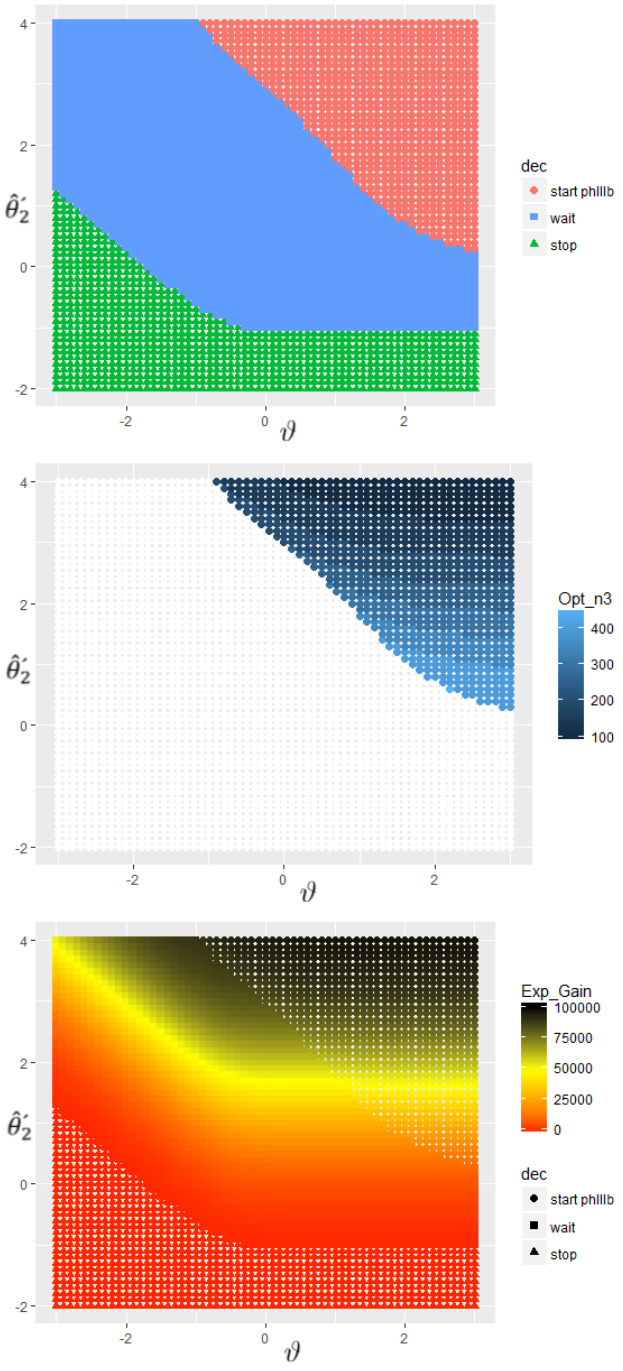

Figure 5-18: Decision 3 in Programme 3 when $\theta \sim N(\vartheta, 1)$, and $\hat{\theta}_2'$ has been observed from the first part of Phase IIIa. The plots show the (top) optimal decisions, (middle) Phase IIIb sample size n_3 if Phase IIIb is started, and (bottom) corresponding expected gain.

Suppose that at Decision 3 in Programme 2, the posterior belief in the true treatment effect is that $\theta \sim N(\vartheta, 1)$. We may ask under what circumstances is it optimal to wait until Decision 4, stop everything, or start Phase IIIb early with a specified n_2? Clearly this will depend upon both the mean of the posterior distribution ϑ and the summary statistic for the first half of Phase IIIa $\hat{\theta}_2'$ as clearly Phase IIIa must be successful in order to realise any revenue.

In Figure 5-18 we analyse the decision rule by varying the values of ϑ and $\hat{\theta}_2'$, and finding the optimal decision in each case. We also record the optimal sample size n_2 for Phase IIIb if one decides to start Phase IIIb early, and record the expected gain in each case.

Figure 5-18 shows that the optimal decision at Decision 3 depends upon both the current beliefs about the true treatment effect and on the observed data so far in Phase IIIa. This is because the observed data from Phase IIIa is to be used in the hypothesis test for Phase IIIa which necessarily needs to result in a rejected null hypothesis for the drug to be successful, as well as the current beliefs about the treatment effect informing how likely one is to observe data that results in rejections of the null hypothesis in both Phase IIIa and IIIb.

5.3 Group sequential Phase III optimisation

Suppose that our Phase III trials may have group sequential designs (GSDs). In this section, we ask which types of GSDs work best when we require two Phase III trials. We will consdier Phase III on its own here rather than as part of a Phase II/III overall design.

Firstly, we consider constructing error spending GSDs in order to satisfy an assurance criterion.

5.3.1 Building error spending designs with an assurance criterion

Classically, error spending designs are constructed subject to a type I error condition under the null hypothesis, and a power requirement under an alternative. In particular, rho-family one sided error spending designs as described in Jennison and Turnbull (2000) with given error spending functions may be constructed given a type I error of 0.025 and power 0.8 at $\theta = 1$. The final information time $I_{\max}$ is then deduced from these requirements.

When constructing the group sequential design, one may perform sensitivity analysis to assess the power of the design under different assumptions about the true treatment effect θ. Based on this logic, it may make sense to construct the design based upon an assurance requirement instead of the power requirement, where the assurance requirement states a particular probability of success given one's current beliefs about the value of θ.

One can do this by constructing an error spending group sequential design such that there is a type I error of α when $\theta = 0$ and there is a probability of rejection of $1 - \beta$ given that $\theta \sim N(\vartheta, \nu^2)$, for some ϑ and ν. In order for such a test to be well defined, it must be the case that the area of the normal distribution to the left of 0 must be less than β. This is the case if

$$\Phi\left(\frac{\vartheta}{\nu}\right) > \beta. \tag{5.22}$$

In Appendix 3.C, we described a method for finding the probability of rejection efficiently

for a group sequential design. Using this method, one may replace the power criterion within the construction of a error spending group sequential design.

5.3.2 Varying the ρ parameter in error spending designs

We identify how the boundaries for a ρ-family error spending group sequential design vary as ρ is changed. We use intuition gained from this to explain results in following sections.

Figure 5-19 shows how the error spending group sequential design shape changes as the parameter ρ is varied. Each subplot is an error spending group sequential design with type I error 0.025 and power 0.8 at $\theta = 1$. Similar shapes are observed when the power requirement is changed to an assurance requirement of probability of rejection 0.8 when θ is distributed according to some normal distribution.

When ρ is low, a large proportion of error is spent on the initial analyses, leading to more frequent early stopping in the first few analyses. However, given the latter stages have less error to spend- this means the information levels between each analysis must be larger.

When ρ is large, a large proportion of error is spent on the latter stages. This produces designs which are unlikely to reject in the early stages, but have relatively low information required to reach the final stage.

Intermediate values of ρ generally strike the optimal balance between error spending in early and late stages and produce designs with the lowest expected information. Commonly used values of ρ are between 1 to 3.

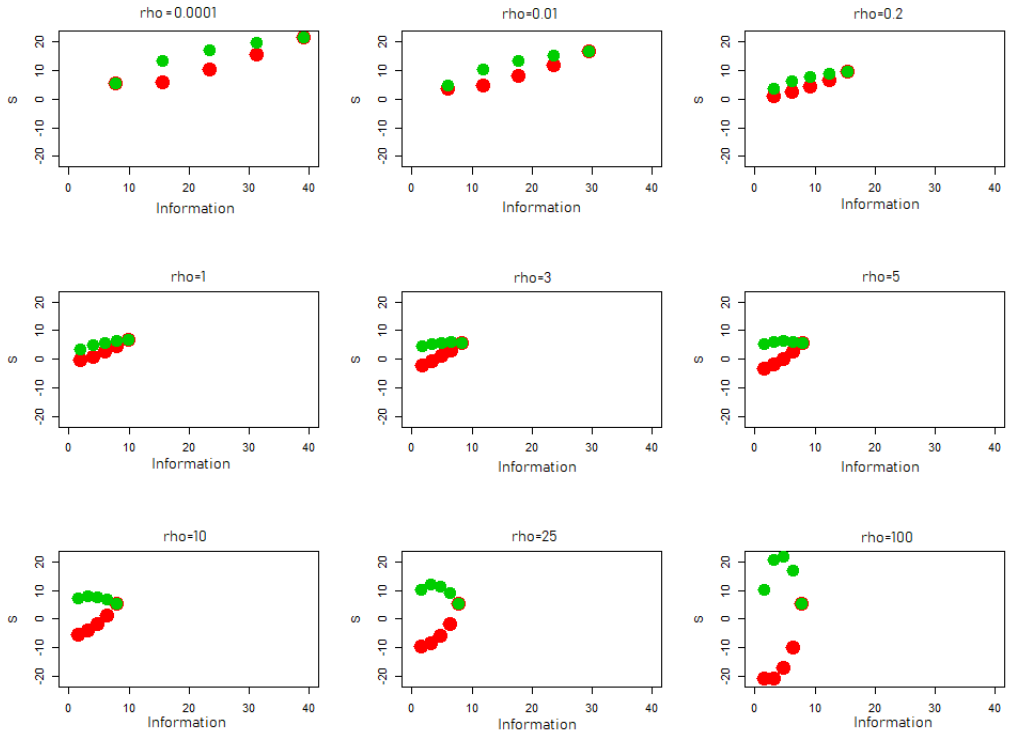

Figure 5-19: Error spending designs with type I error 0.025 and power 0.8 at $\theta = 1$, as the parameter ρ varies.

5.3.3 Two error spending Phase III designs

Suppose one constructs a group sequential test with K analyses. Under particular assumptions about θ, define the random variable of the time one terminates the group sequential test as $\mathcal{I}^{(\text{obs})}$.

The probability mass function of $\mathcal{I}^{(\text{obs})}$ may be denoted as $\pi_k := \mathbb{P}(\mathcal{I}^{(\text{obs})} = k)$, where $\sum_{k=1,...,K} \pi_k = 1$. These probabilities are obtained as by-products from the calculations required to construct the group sequential test.

Given that there are two independent identical group sequential designs running in parallel, the distribution of the maximum of the times one terminates the group sequential test may be deduced. Denote the random variable

$$\mathcal{I}'^{(\text{obs})} = \max(\mathcal{I}_1^{(\text{obs})}, \mathcal{I}_2^{(\text{obs})}), \tag{5.23}$$

where $\mathcal{I}_1^{(\text{obs})}$ and $\mathcal{I}_2^{(\text{obs})}$ are independent and identically distributed.

One may show that

$$\begin{aligned} &\pi'_1 = \pi_1^2, \text{ and} \\ &\pi'_k = 2\pi_k \sum_{i=1}^{k-1} \pi_i + \pi_k^2 \quad \text{for } k = 2, ..., K. \end{aligned} \tag{5.24}$$

Using the distribution defined by these probabilities, one may easily calculate the expected sample size of the longer of two independent but identically defined group sequential designs.

In the figures below, we look at how the value of ρ affects the expected sample size of an individual group sequential design and the longer of two GSDs, under different assumptions about the treatment effect θ.

Figures 5-20 and 5-21 show that the optimal value of ρ to minimise the expected information varies, depending on whether Phase III consists of one or two GSDs and under what treatment effect θ the expected information is calculated.

Figure 5-20 in particular shows for poor treatment effects, a low ρ allows lots of error to be spent in the early stages, making early rejection more likely. This is even more so the case when one considers two Phase III GSDs, where the optimal ρ is even lower than the single Phase III counterpart. What is more interesting, is when the treatment effect is high. In this case one desires a larger ρ value. Again, this is even more so the case when we consider two Phase III GSDs, with the optimal ρ even higher than the single Phase III counterpart. But the optimal ρ for a single GSD does well for the two GSD case.

Figure 5-21 shows the dependence on ρ when $\theta \sim N(1, 0.5^2)$. This prior involves a mix of the effects observed in Figure 5-20, as it contains both low and high values of θ. In this case the optimal ρ is a moderate value with the two Phase III group sequential design counterpart having a slightly higher optimal value of ρ. GSDs with these values of ρ are shown in the figure below.

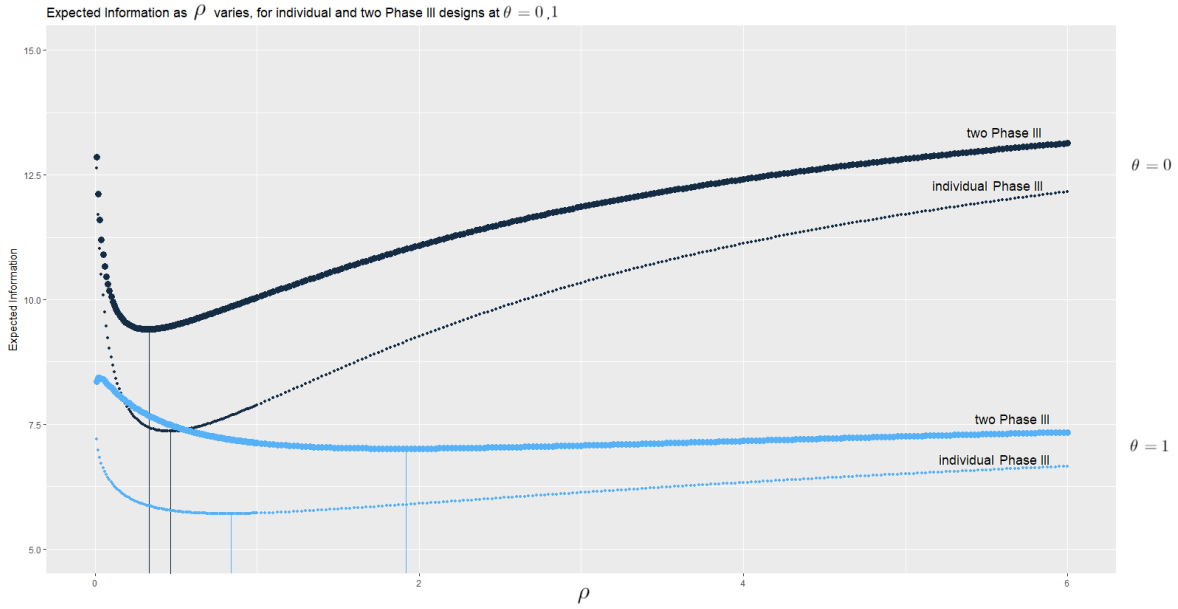

Figure 5-20: Thin dark blue: Expected information when $\theta = 0$ for an individual Phase III group sequential design. Thick dark blue: Expected information when $\theta = 0$ for a pair of Phase III GSDs. Thin light blue: Expected information when $\theta = 1$ for an individual Phase III group sequential design. Thick light blue: Expected information when $\theta = 1$ for a pair of Phase III GSDs. Vertical lines show the minimum of each curve. GSDs are defined to have power 80% at $\theta = 1$.

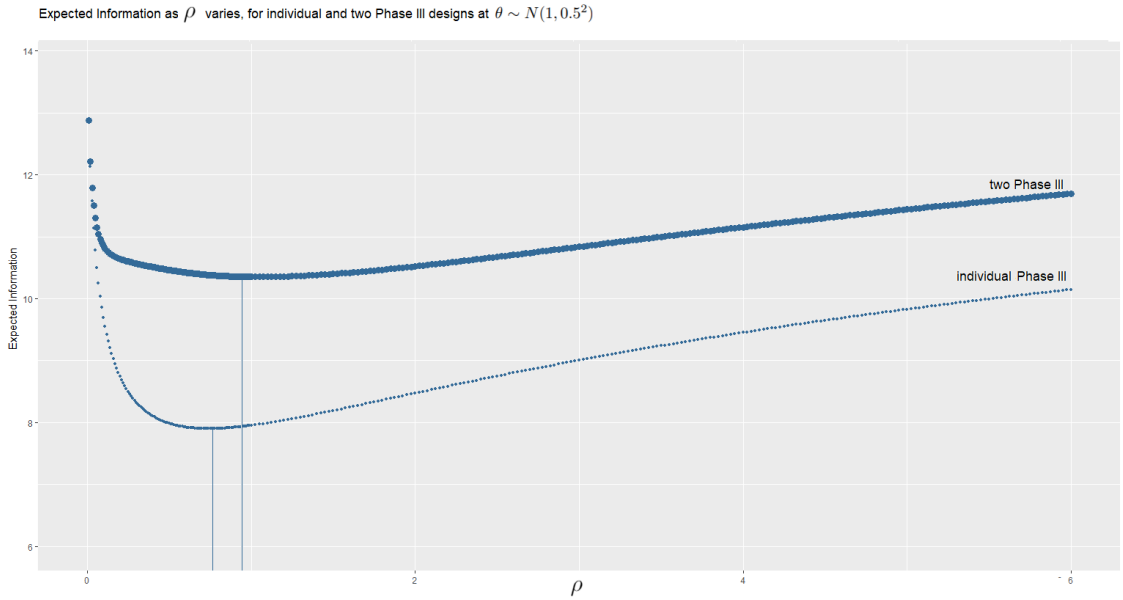

Figure 5-21: Thin curve: Expected information when $\theta \sim N(1, 0.5^2)$ for an individual Phase III group sequential design. Thick curve: Expected information when $\theta \sim N(1, 0.5^2)$ for a pair of Phase III GSDs. Vertical lines show the minimum of each curve. GSDs are constructed to have assurance of 80% when $\theta \sim N(1, 0.5^2)$.

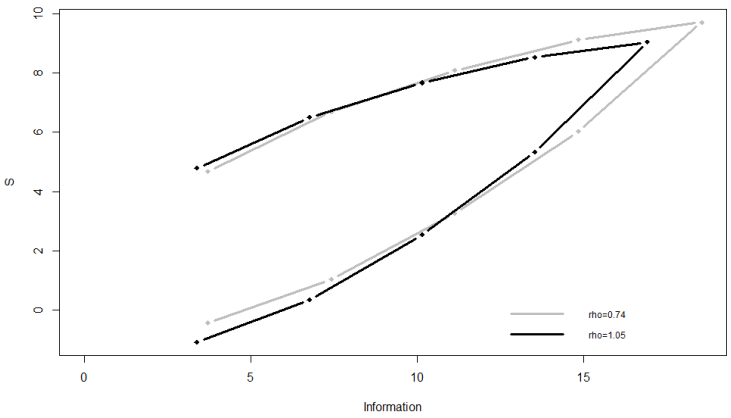

Figure 5-22: Optimal Error Spending Group Sequential Boundaries for 1 Phase III (grey), with $\rho = 0.74$, and 2 Phase IIIs (black), with $\rho = 1.05$.

5.4 Discussion

We have attempted to tackle the problem of how best to perform two Phase III trials. We have found that the answer often depends upon the assumptions made about the drug, such as the magnitude of various costs and revenues, and assumptions about the drug's efficacy.

From our first simulation study, we find that the best way to perform the two Phase III trials depends upon the parameters of the drug and the posterior distribution of the treatment effect after Phase II. In the case when testing the drug is expensive or the time to treat patients is low, or when one is more pessimistic about the treatment effect, one favours taking the trials sequentially in order to make more informed decisions about investing in the Phase IIIb trial. The adaptive programme from the second simulation study is a compromise between the two original programmes and adds value in certain combinations of drug parameters and beliefs about the treatment effect.

Discussions with sponsors suggest the parallel approach is most commonly used in industry. It may be the case that drugs that have appeared in industry have parameter values and beliefs about the treatment effect that more commonly favour the parallel approach. That is, they are optimistic about the drugs treatment effect (otherwise one may not take the drug forward at all). The approach taken here to derive optimal decision rules for programmes and compare optimised programmes against each other can be applied in practice, in situations where the parameters are better known. This approach may then be used to inform and justify high value decisions about how a programme of trials are performed.

The work on two group sequential designs provides an initial starting point to gain intuition as to the appropriate types of GSDs to use in the two Phase III trial scenario. Whether one should spend error later or earlier depends upon whether the treatment effect is low or high. In the case when there is uncertainty as to the treatment effect, but it is thought to be positive, the optimal value of group sequential design parameter ρ when performing two Phase III trials was found to be close to the optimal value of that for only one group sequential trial in our example. Whilst the choice of ρ for a set of two Phase III group sequential design trials may not necessarily need to be optimised for each trial, the intuitions gained from these results may help aid an appropriate selection.

6 The Portfolio Problem

6.1 The Portfolio Problem

The portfolio problem concerns a portfolio of drugs in development, and the optimal allocation of a research and development budget to develop these drugs.

Suppose a portfolio of drugs are in development. Suppose these drugs are in development stages prior to Phase III commencing, which may include Phase II, I, or pre-clinical studies. Based on current knowledge, it is believed these drugs have some prior probability of being efficacious and have some probability of successfully reaching Phase III at some time point in the future.

Once a drug becomes available for Phase III, there may be different Phase III design options for that drug. Different design options may use up different amounts of budget whilst affecting the probability of the drug passing Phase III successfully. The portfolio problem is to find the optimal Phase III design for each drug given what has happened in the portfolio so far.

Formulation

Suppose there are I drugs in the portfolio and let the total budget be denoted by $\mathcal{B}_{\text{PortTot}}$. Suppose the patient responses for drug i and control are normally distributed with known variance σ^2. Denote by θ_i the treatment difference between drug i and control. We are interested in testing the hypothesis that $H_{0,i} \ : \ \theta_i \leq 0$ for each drug i. We suppose the one-sided type I error rate for drug i is given by α_i.

We say that drug i is due to become *available* for Phase III at a particular time when the drug has had a technical success in Phase II and is ready to start Phase III. Assume drug i is available for Phase III at $t_i^{(a)}$, and the probability of the drug being available for Phase III development at this time is $p_i^{(a)}$. Time $t_i^{(a)}$ is the only time drug i can become available for Phase III. Probability $p_i^{(a)}$ therefore represents the probability of drug i having a technical success in Phase II and proceeding to Phase III.

If drug i is available for Phase III, current knowledge about the treatment effect, θ_i, suggests it may take $\theta_i = \mu_i^1$ in an efficacious scenario and $\theta_i = \mu_i^0$ in a non-efficacious scenario. Conditional on drug i being available, we give θ_i a two point prior with density π such that

$$\begin{aligned} \pi(\mu_i^0) &= p_i^{\text{eff}}, \text{ and} \\ \pi(\mu_i^1) &= 1 - p_i^{\text{eff}}, \end{aligned} \tag{6.1}$$

for some probability p_i^{eff}.

For each drug i, we require n_i^{trials} confirmatory trials in Phase III, all of which need to be successful for the drug to be marketed. This will generally be either 1 or 2.

For drug $i = 1, ..., I$, there are J_i designs for each Phase III trial one may choose from (including not performing Phase III at all) each with power $1 - \beta_{i,j}$ and corresponding total sample size $n_{i,j}$ for $j = 1, ..., J_i$. If $n_i^{\text{trials}} > 1$, then all trials for drug i must have the same design. The probability a trial is a success in Phase III is

$$PoTS_{i,j} = (1 - \beta_{i,j})p_i^{\text{eff}} + \alpha_i(1 - p_i^{\text{eff}}). \tag{6.2}$$

Given there are n_i^{trials} Phase III trials for drug i, the overall probability of success is $PoS_{i,j}$, given by

$$PoS_{i,j} = (1 - \beta_{i,j})^{n_i^{\text{trials}}} p_i^{\text{eff}} + \alpha_i^{n_i^{\text{trials}}}(1 - p_i^{\text{eff}}). \tag{6.3}$$

The total cost of the Phase III trials for drug i and design j is defined as $b_{i,j}$. In the case of fixed sample designs, this is a fixed quantity. In the case of group sequential designs, $b_{i,j}$ is a random variable which depends upon the analysis at which the design terminates. The expected gain for drug i and design j is defined as $e_{i,j}$ which depends upon $PoS_{i,j}$. The gain function that is used to calculate $b_{i,j}$ and $e_{i,j}$ is discussed in the next section.

Below, we list the notation to be used in this chapter.

Portfolio Problem Definition List

I	Number of drugs in the portfolio.
α_i	Type I error rate for drug i.
J_i	Number of possible designs for drug i.
μ_i^1	Value of true treatment effect θ_i when drug i is efficacious.
μ_i^0	Value of true treatment effect θ_i when drug i is not efficacious.
σ_i^2	Response variance for drug i.
$\beta_{i,j}$	Type II error rate for drug i with design j when $\theta_i = \mu_i^1$.
$n_{i,j}$	Total sample size required for each Phase III trial with drug i, design j. Deduced from other parameters such as $\beta_{i,j}$, α_i, and σ_i^2.
$b_{i,j}$	Budget required for each Phase III trial with design j on drug i (\$M).
$PoST_{i,j}$	The probability of success (rejection of the null hypothesis) for each Phase III trial with design j for drug i.
n_i^{trials}	Number of successful trials required for Phase III for drug i to market the drug.
$PoS_{i,j}$	The probability of success of all n_i^{trials} trials for drug i.
$e_{i,j}$	Expected gain from drug i with design j (\$M).
$\mathcal{B}_{\text{PortTot}}$	Total portfolio budget.
θ_i	True treatment effect for drug i.
$t_i^{(a)}$	Time of availability of drug i.
$p_i^{(a)}$	Probability of availability of drug i.
p_i^{eff}	Probability that drug i is efficacious.

Financial model Definition List

f_i	Fixed cost incurred per fixed sample Phase III trial ($M).
c_i	Cost per patient in a Phase III trial ($M).
λ_i	Recruitment rate for drug i (patients/month).
$t_i^{\mathbf{trt}}$	Time to treat and observe the response of 1 patient (months).
F_i	Fixed marketing set up cost ($M).
t_i^s	Set up time between the end of Phase III and first sales (months)
T_i^P	Time at which the patent for drug i expires from time 0 (months).
ρ	Monthly discount rate.
$R_i^{\mathbf{mean}}$	Mean revenue per month for drug i ($M).
$R_i^{\mathbf{sd}}$	Standard deviation of R_i^{mean} ($M).

The Financial Model

The gain function defines the value of a pharmaceutical asset to the sponsor from which one may derive the optimal decisions within the portfolio. Changing the gain function changes the exact question the portfolio problem asks. As introduced in Section 1.5.1 and with similar forms used in Sections 3.5.1, 5.1.2, and 7.4, we consider the Financial Model, a gain function which aims to model the expected net present value of a drug. In contrast to the other approaches, the financial model is defined for each drug in our portfolio, so the gain for the portfolio problem is the sum of the individual gains from each drug $i = 1, ..., I$. In the text below, we outline the financial model for drug i illustrated in Figure 6-1.

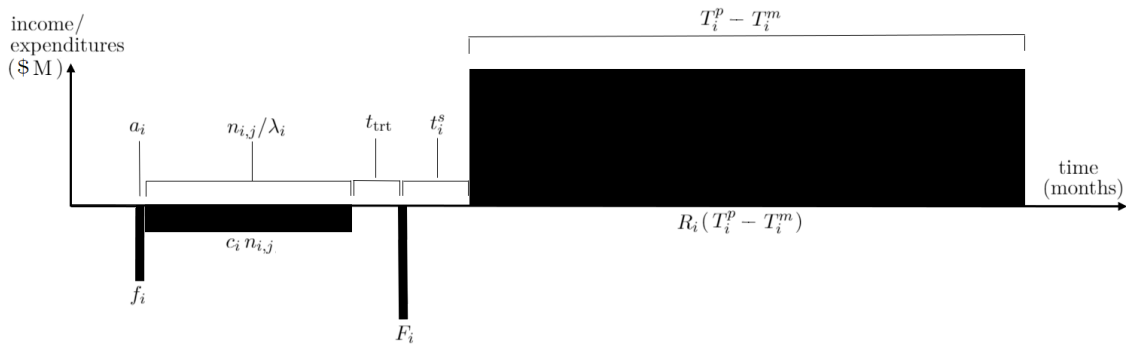

Figure 6-1: Schematic of the financial model for a single Phase III trial of drug i with design j, assuming Phase III is successful with revenue per month R_i. Quantities above the x-axis denote time intervals or times events occur, and below the x-axis denote incomes and expenditure amounts.

The financial model specifies the incomes and expenditures of drug i with a particular design in $M. The initial expenditures consist of a fixed cost f_i per Phase III trial and a patient recruitment cost of c_i per patient. The patients are recruited at a rate of λ_i patients/month and each patient takes t_i^{trt} months to be treated and have an observed response. The total time for a Phase III trial with $n_{i,j}$ patients is thus $n_{i,j}/\lambda_i + t_i^{\text{trt}}$ months.

The n_i^{trials} Phase III trials for drug i are all performed in parallel. If at least one of the trials is not successful, no further incomes or expenditures are realised. Assuming all the Phase III trials were successful, a fixed marketing set up cost of F_i is incurred, followed by a time period of t_i^s allowing for production, distribution, and sales set up. Denote this time point $T_i^m = t_i^{(a)} + n_{i,j}/\lambda_i + t_i^{\text{trt}} + t_i^s$. From this time point until the time of patent expiry, denoted by T_i^p, the drug may be marketed. During this marketing time, an income per month R_i is realised, representing the time the drug can be sold with exclusivity in its target market. This revenue per month is sampled using a normal random variable for each drug with mean R_i^{mean} and standard deviation R_i^{sd} to represent the uncertainty of the commercial success of the marketed drug. Once the patent expires and the drug finishes its exclusivity period, we assume no further incomes or expenditures are incurred.

We discount future costs and revenues continuously at rate ρ. This is a common approach in portfolio modelling and represents inflation and the opportunity cost.

- If design j is fixed sample:

For any available drug i and design j, we define the budget, that is, the financial cost to perform Phase III, as

$$b_{i,j} := n_i^{\text{trials}}\ f_i\ \exp(-\rho t_i^{(a)}) + (n_i^{\text{trials}}\ c_i\ \lambda_i) \int_{t_i^{(a)}}^{t_i^{(a)}+n_{i,j}/\lambda_i} \exp(-\rho t) dt, \tag{6.4}$$

and the financial gain of a successful Phase III (where all Phase III trials reject the null hypothesis) as

$$r_{i,j} := -b_{i,j} - F_i\ \exp(-\rho(t_i^{(a)} + n_{i,j}/\lambda_i + t_i^{\text{trt}})) + R_i \int_{T_i^m}^{T_i^p} \exp(-\rho t) dt. \tag{6.5}$$

When drug i is available and has design j, the financial gain for drug i is therefore defined as

$$\mathcal{G}_{i,j} := \mathbb{1}_{(\text{Phase III successful})}\ r_{i,j}\ -\ \mathbb{1}_{(\text{Phase III unsuccessful})}\ b_{i,j}. \tag{6.6}$$

The financial gain of the portfolio $\mathcal{G}$ with drugs $i = 1, ..., I$ with designs $j_1, j_2, ..., j_I$ respectively may be then defined as

$$\mathcal{G} := \sum_{i=1}^{I} \mathcal{G}_{i,j_i}. \tag{6.7}$$

Let the expected financial gain of available drug i with design j when Phase III is not successful be denoted by $e_{i,j}^{\text{NOSUCCESS}}$. Similarly when Phase III is successful, we denote this by $e_{i,j}^{\text{SUCCESS}}$. Overall, the expected financial gain of available drug i with design j is denoted by $e_{i,j}$. Then as $b_{i,j}$ is a-priori known, $e_{i,j}^{\text{NOSUCCESS}} = -b_{i,j}$ and

$$e_{i,j}^{\text{SUCCESS}} = -b_{i,j} - F_i\ \exp(-\rho(t_i^{(a)} + n_{i,j}/\lambda_i + t_i^{\text{trt}})) + R_i^{\text{mean}} \int_{T_i^m}^{T_i^p} \exp(-\rho t) dt, \tag{6.8}$$

and

$$e_{i,j} = PoS_{i,j}\ e_{i,j}^{\text{SUCCESS}}\ +\ (1 - PoS_{i,j})\ e_{i,j}^{\text{NOSUCCESS}}. \tag{6.9}$$

- If design j is group sequential:

Then each trial sample size is also a random variable depending upon at which analysis the trial terminates. We adapt the above equations for group sequential designs. Consider the n_i^{trials} trials for drug i. We make two simplifying assumptions about the group sequential designs.

Firstly, we make the assumption that all group sequential trials run independently until they terminate and Phase III concludes when the final group sequential trial terminates. In particular, trials continue even if another has stopped for futility. Secondly, we assume that at each interim analysis, the responses of all patients that have been recruited for the trial by that time point are used in the interim analysis. This assumption assumes the treatment time and time to response is small enough that nearly all patients recruited by the time of the interim analysis have responses that may be used in the interim analysis.

For the rth group sequential trial for drug i with design j, let $n_{i,j}^{(r)}$ be the observed sample size upon termination for $r = 1, ..., n_i^{\text{trials}}$. That is, if the group sequential design has K_i analyses, $n_{i,j}^{(r)}$ may take K_i possible values for each r, i, and j. Given the properties of the group sequential design and the prior on the treatment effect, one may calculate the probability of observing sample sizes upon termination for each trial $\boldsymbol{n}_{i,j} := (n_{i,j}^{(1)}, ..., n_{i,j}^{(n_i^{\text{trials}})})$ denoted by $p_{\boldsymbol{n}_{i,j}}$. The sample sizes upon termination for each trial are conditionally independent given the treatment effect, so these probabilities may be calculated with ease.

We define $b_{i,j}^{(\boldsymbol{n}_{i,j})}$, $r_{i,j}^{(\boldsymbol{n}_{i,j})}$, and $\mathcal{G}_{i,j}^{(\boldsymbol{n}_{i,j})}$ as the financial cost of performing Phase III, the financial gain of a successful Phase III, and the overall financial gain given sample sizes upon termination of $\boldsymbol{n}_{i,j}$. The financial cost of an unsuccessful Phase III is

$$b_{i,j}^{(\boldsymbol{n}_{i,j})} := n_i^{\text{trials}} \; f_i \; \exp(-\rho t_i^{(a)}) + \sum_{r=1}^{n_i^{\text{trials}}} c_i \; \lambda_i \int_{t_i^{(a)}}^{t_i^{(a)} + n_{i,j}^{(r)}/\lambda_i} \exp(-\rho t) dt, \tag{6.10}$$

and the gain give a successful Phase III is

$$r_{i,j}^{(\boldsymbol{n}_{i,j})} := -b_{i,j}^{(\boldsymbol{n}_{i,j})} - F_i \; \exp(-\rho(t_i^{(a)} + \max_r(n_{i,j}^{(r)})/\lambda_i + t_i^{\text{trt}})) + R_i \int_{T_{i,r}^m}^{T_i^p} \exp(-\rho t) dt, \tag{6.11}$$

where $T_{i,r}^m$ is defined as $T_{i,r}^m := T_i^m = t_i^{(a)} + \max_r(n_{i,j}^{(r)})/\lambda_i + t_i^{\text{trt}} + t_i^s$. We adapt Equation 6.6 from the fixed sample case to get

$$\mathcal{G}_{i,j}^{(\boldsymbol{n}_{i,j})} := \mathbb{1}_{(\text{Phase III successful})} \; r_{i,j}^{(\boldsymbol{n}_{i,j})} \; - \; \mathbb{1}_{(\text{Phase III unsuccessful})} \; b_{i,j}^{(\boldsymbol{n}_{i,j})}. \tag{6.12}$$

Furthermore, we define the budget $b_{i,j}$ for drug i and design j assuming all group sequential trials run until their final analyses,

$$b_{i,j} := \max_{\boldsymbol{n}_{i,j}} (b_{i,j}^{(\boldsymbol{n}_{i,j})}) \tag{6.13}$$

We make a commitment to this budget, but may not use it all if trials stop early.

The financial gain of the portfolio $\mathcal{G}$ with drugs $i = 1, ..., I$ with designs $j_1, j_2, ..., j_I$ respectively may be then defined as

$$\mathcal{G} := \sum_{i=1}^{I} \mathcal{G}_{i,j_i}^{\boldsymbol{n}_{i,j_i}}. \tag{6.14}$$

As in the fixed sample case, define $e_{i,j}^{\text{NOSUCCESS}}$, $e_{i,j}^{\text{SUCCESS}}$, and $e_{i,j}$ respectively. These take the form

$$e_{i,j}^{\text{NOSUCCESS}} = -\sum_{\boldsymbol{n}_{i,j}} p_{\boldsymbol{n}_{i,j}} b_{i,j}^{(\boldsymbol{n}_{i,j})}, \tag{6.15}$$

and

$$\begin{aligned} e_{i,j}^{\text{SUCCESS}} := \sum_{\boldsymbol{n}_{i,j}} p_{\boldsymbol{n}_{i,j}} \Bigg[& - b_{i,j}^{(\boldsymbol{n}_{i,j})} - F_i \exp(-\rho(t_i^{(a)} + \max_r(n_{i,j}^{(r)})/\lambda_i + t_i^{\text{trt}})) \\ & + R_i^{\text{mean}} \int_{T_{i,r}^m}^{T_i^p} \exp(-\rho t) dt \Bigg]. \end{aligned} \tag{6.16}$$

The expected financial gain $e_{i,j}$ is as in the fixed sample case given by

$$e_{i,j} = PoS_{i,j}\ e_{i,j}^{\text{SUCCESS}}\ +\ (1 - PoS_{i,j})\ e_{i,j}^{\text{NOSUCCESS}}. \tag{6.17}$$

Computing the optimal decisions

The best design for a particular drug will depend upon the total budget remaining, the designs that were used for previous drugs, and the drugs that may be available for investment in the future. In the following sections, we outline methods that may be used to calculate the optimal decisions and total portfolio value. In Section 6.2 we describe an integer programming method for solving the portfolio problem. In Section 6.3 we describe the dynamic programming method applied with the *design history* state space in Section 6.3.1 and with the *budget remaining* state space in Section 6.3.2.

6.2 The integer programming method

The integer programming method formulates the portfolio problem as a stochastic integer programming problem, and calls an integer programming solver to produce solutions. This approach was used by Patel et al. (2013), motivated by previous approaches such as Gatica et al. (2003), Colvin and Maravelias (2008), Varma et al. (2008), and Solak et al. (2010) which either used integer programming, stochastic integer programming, or simulation based approaches. All these approaches consider fixed sample designs only. In this section, we outline the Patel et al. (2013) integer programming approach for the problem.

The method makes use of availability histories and decision variables. The availability history describes which drugs in the past were available or not, with $a_i = 1$ denoting drug i being available and $a_i = 0$ denoting drug i not being available. Suppose for simplicity and without loss of generality that the probability of availability of Drug 1 is $p_1^{(a)} = 1$. The availability history of $a_2, ..., a_{i-1}$ has corresponding probability $\prod_{m=2}^{i-1} (p_m^{(a)})^{a_m} (1 - p_m^{(a)})^{1-a_m}$. Decision variables describe the overall strategy of the portfolio and are defined for each drug with a certain availability history.

Define decision variables

$$Z_{1,j} = \begin{cases} 1 & \text{Design } j \text{ is used for Drug 1 if it is available} \\ 0 & \text{otherwise,} \end{cases} \tag{6.18}$$

and for $i = 2, ..., I$

$$Z_{i,j|a_2,...,a_{i-1}} = \begin{cases} 1 & \text{if drug } i \text{ uses design } j \text{ given availability history } a_2, ..., a_{i-1}. \\ 0 & \text{otherwise.} \end{cases} \tag{6.19}$$

The integer programming method formulates the problem by requiring one to find the decision variables to maximise the expected gain of the portfolio

$$p_1^{(a)} \sum_j e_{1,j} Z_{1,j} + \sum_{i=2}^{I} \sum_{a_1} \sum_{a_2} ... \sum_{a_{i-1}} p_i^{(a)} \prod_{m=2}^{i-1} (p_m^{(a)})^{a_m} (1-p_m^{(a)})^{1-a_m} \sum_j e_{i,j} Z_{i,j|a_1,a_2,...,a_{i-1}}, \tag{6.20}$$

subject to design constraints

$$\begin{aligned} \sum_j Z_{i,j} &\leq 1 \text{ for } i = 1 \\ \sum_j Z_{i,j|a_2,...,a_{i-1}} &\leq 1 \text{ for } i = 2, 3, ..., I, \text{ and any } a_1, ..., a_{i-1}, \end{aligned} \tag{6.21}$$

and budget constraints detailing the budget to be used at time points during the portfolio, ensuring that the strategy does not use more than the available budget. See Patel et al. (2013) for further details.

The integer programming method formulates the problem in the following form

$$\begin{aligned} &\text{Maximise } \boldsymbol{cZ} \\ &\text{subject to } A\boldsymbol{Z} \leq \boldsymbol{b}. \end{aligned} \tag{6.22}$$

One may store A as a sparse matrix and call an integer programming solver to compute the solution.

As the number of drugs in the portfolio increases, the size of the integer programming problem becomes very large. In Section 6.4, we show the size of the portfolio that this method may find the optimal decisions in a reasonable amount of time. In particular, if all drugs have uncertainty as to whether they will become available or not, we find that the method can handle up to 8 drugs in a reasonable amount of time. In addition, this formulation only allows the designs of each drug to be fixed sample. It is not clear how this formulation would be extended to allow group sequential methods.

6.3 The dynamic programming method

In Section 1.4 we introduced the method of dynamic programming for computing optimal decisions in a process. In this section, we show how dynamic programming can be used to tackle the portfolio problem.

Suppose at the time drug i becomes available there are states s_i that one may find themselves at. These states relate to what has happened previously in the portfolio. Define $\mathcal{E}_i(s_i)$ as the expected gain from drugs $i, i+1, ..., I$, given one is at state s_i and one chooses optimal designs for the remainder of the portfolio. The value this quantity takes at drug $i = 1$ at the initial state can be considered the value of the portfolio. Dynamic programming computes these values iteratively drug by drug, starting at $i = I$ and working backwards, breaking down the large problem of calculating this quantity at the first drug into smaller sub-problems.

An important part of the method is the need for a dynamic programming *central equation*. In dynamic programming literature, this may be called the Bellman Equation as in Bellman (1957). The idea involves having the sub-problems nested recursively inside a larger problem by having an equation define a relation between the larger problem and the sub-problems. In particular in this context, the equation expresses the expected gain from drugs $i, i+1, ..., I$ in terms of the expected gain from drugs $i+1, ..., I$. That is, the quantity $\mathcal{E}_i(s_i)$ is expressed in terms of $\mathcal{E}_{i+1}(s_{i+1})$ for different possible states s_{i+1}.

Consider the value of $\mathcal{E}_I(s_I)$ at the final drug I for some s_I. Finding the optimal design and corresponding expected gain is trivial in this case: the optimal design is the design in the set of all the designs one can afford which produces the largest expected net present value. Using the *central equation*, the problem at drug $I-1$ of computing $\mathcal{E}_{I-1}(s_{I-1})$ for some s_{I-1} may be solved by reading solutions of the already solved sub-problem at drug I. One may repeat this for each state s_{I-1} at drug $I-1$, and then work backwards drug by drug until Drug 1.

6.3.1 The dynamic programming on a design history state space method

In this section, we illustrate how the dynamic programming method with a design history state space can be used to solve the portfolio problem. As in the stochastic integer programming method in Section 6.2, we restrict our attention to fixed sample designs only.

Method

Define a state at drug i in the portfolio as the design history $j_1 j_2 ... j_{i-1}$, with j_r representing the design chosen for drug r for $1 \leq r \leq i-1$. Let $\mathcal{E}_i(j_1 j_2 ... j_{i-1})$ denote the expected gain from drugs i to I, given one is at state $j_1 j_2 ... j_{i-1}$ at drug i, and one makes decisions optimally for the remainder of the portfolio. Define $\mathcal{J}_{i,j_1 j_2 ... j_{i-1}}$ as the set of possible designs one can afford for drug i given how much of the budget has been used on designs specified by $j_1 j_2 ... j_{i-1}$.

For any drug $i = 1, ..., I-1$, state $j_1 j_2 ... j_{i-1}$, if design $j \in \mathcal{J}_{i,j_1 j_2 ... j_{i-1}}$ is chosen for drug i, the state at drug $i+1$ is $j_1 j_2 ... j_{i-1} j$. If drug i is not available for Phase III, then the design for drug i is necessarily $j = 1$.

In the next equations, we formulate the dynamic programming *central equations*:

$$\mathcal{E}_I(j_1 j_2 ... j_{I-1}) = p_I^{(a)} \max_{j \in \mathcal{J}_{I,j_1 j_2 ... j_{I-1}}} e_{I,j}, \tag{6.23}$$

and for $i = 1, ..., I-1$,

$$\mathcal{E}_i(j_1 j_2 ... j_{i-1}) = p_i^{(a)} \max_{j \in \mathcal{J}_{i,j_1 j_2 ... j_{i-1}}} \left[e_{i,j} + \mathcal{E}_{i+1}(j_1 j_2 ... j_{i-1} j) \right] + (1 - p_i^{(a)})\ \mathcal{E}_{i+1}(j_1 j_2 ... j_{i-1} 1). \tag{6.24}$$

We note that Equation 6.24 has the form of the Bellman Equation (as in Bellman (1957)). The expected value at a particular state at one stage ($\mathcal{E}_i(j_1 j_2 ... j_{i-1})$) is written in terms of the expected value at different states at the next stage ($\mathcal{E}_{i+1}(j_1 j_2 ... j_{i-1} j)$ for different j) in this equation.

Dynamic Programming (Design History) Definition List

$j_1 j_2 ... j_{i-1}$	State describing the design history at drug i in the portfolio.
$\mathcal{E}_i(j_1 j_2 ... j_{i-1})$	Expected gain of drugs i to I given remaining budget $j_1 j_2 ... j_{i-1}$ at drug i.
$\mathcal{J}_{i,j_1 j_2 ... j_{i-1}}$	Possible designs one can afford at drug i given a design history of $j_1 j_2 ... j_{i-1}$.

Implementation

In this section we describe the algorithms to compute the optimal decisions in the portfolio as pseudo-code.

STEP 1: Gather inputs

- Portfolio inputs

$I,\ \alpha_i,\ J_i,\ \beta_{i,j},\ n_i^{\text{trials}},\ \mathcal{B}_{\text{PortTot}},\ \sigma_i^2,\ t_i^{(a)},\ p_i^{(a)},\ p_i^{\text{eff}},\ \mu_i^1,\ \mu_i^0$ for all appropriate i, j.

- Financial model inputs

$f_i,\ c_i,\ \lambda_i,\ t_{\text{trt}},\ F_i,\ t_i^s,\ T_i^p,\ \rho$ for all appropriate i.

STEP 2: Compute Designs

In this step, we use the financial model and portfolio inputs to calculate the budget and expected gain for each drug and design. As we are only considering fixed sample designs, the budget is a-priori known for each drug i and design j.

- For every possible drug and design, we calculate the:
  - Budgets $b_{i,j}$ and expected gain $e_{i,j}$ for each $i = 1, ..., I$ and $j = 1, ..., J_i$ using the Financial Model equations of Section 6.1.

List the inputs and designs in object $\mathfrak{I} := \{I,\ \mathcal{B}_{\text{PortTot}},\ (\mathfrak{I}_i)_{\{i=1,...,I\}}\}$, where
$\mathfrak{I}_i = \{p_i^{(a)}, (b_{i,j})_{\{j=1,...,J_i\}},\ (e_{i,j})_{\{j=1,...,J_i\}},\ n_i^{\text{trials}}\}$.

STEP 3: Initial Computations

Firstly, for efficiency, remove designs that have higher budgets and lower expected gains than another design for the same drug.

The method of dynamic programming is to work backwards, drug by drug, finding the optimal decisions for any possible design history. This works because the optimal decisions for a particular drug depend only on the current state, as specified in Equation 6.24.

For the optimal decision at each state at drug i, the corresponding eNPV can be stored in a large array `eG_Arr`, where the entry with index j_1,j_2,...,j_{i-1} gives the eNPV of drug i and the remainder of the portfolio of the optimal design at drug i given a design history of $j_1 j_2 ... j_{i-1}$.

In the algorithms below, we summarise the method used to calculate the optimal decisions for the portfolio.

STEP 4: Dynamic Programming Algorithm

The following boxes contain the algorithms used to perform the dynamic programming method.

```
Master_Function

Inputs: ℑ, eG_Arr

for i in I,I − 1,...,1
        eG_Arr ← Update_Opt_Decs (i, eG_Arr)
end for loop
Return eG_Arr
```

```
Update_Opt_Decs

Inputs: i, eG_Arr

for every combination j_1 j_2 ... j_{i−1} of possible design histories
        Calculate the optimal design j* and corresponding e_{i,j*}
        given a design history j_1 j_2 ... j_{i−1} using Equation 6.24.
        This involves reading stored elements in eG_Arr for the next drug.
        j_1, ..., j_{i−1}th entry of eG_Arr ← e_{i,j*}.
end for loop
Return eG_Arr
```

6.3.2 The dynamic programming on a budget remaining state space method

In this section, we illustrate how the dynamic programming method with a budget remaining state space can be used to solve the Portfolio Problem. This differs to the design history state space approach by defining states as the budget remaining for the remainder of the portfolio rather than the design history of previous drugs. As before, we restrict our attention to designs that are fixed sample.

Method

Define the current state to be $\mathcal{B}$ if there is a remaining budget of $\mathcal{B}$ at this time. If one is at state $\mathcal{B}$ at drug i, one has a a total portfolio budget of $\mathcal{B}$ remaining to spend on drugs $i, i+1, ..., I$. Let $\mathcal{E}_i(\mathcal{B})$ denote the sum of the expected value of the gain function of drugs i to I, given one is at state $\mathcal{B}$ at drug i, and one makes decisions optimally. Define $\mathcal{J}_{i,\mathcal{B}}$ as the set possible designs one can afford for drug i given a remaining budget of $\mathcal{B}$.

For any state $\mathcal{B}$, drug $i = 1, ..., I-1$ and design $j \in \mathcal{J}_{i,\mathcal{B}}$, the only possible state for drug $i+1$ is $\mathcal{B} - b_{i,j}$ if the drug is available. That is, given one is at drug i with total budget $\mathcal{B}$ and one chooses design j, one would move to state $\mathcal{B} - b_{i,j}$ at drug $i+1$.

We formulate the dynamic programming *central equations*. For the last drug, drug I, we have

$$\mathcal{E}_I(\mathcal{B}) = p_i^{(a)} \max_{j \in \mathcal{J}_{I,\mathcal{B}}} e_{i,j}, \tag{6.25}$$

and for $i = 1, ..., I-1$,

$$\mathcal{E}_i(\mathcal{B}) = p_i^{(a)} \max_{j \in \mathcal{J}_{i,\mathcal{B}}} \left[e_{i,j} + \mathcal{E}_{i+1}(\mathcal{B} - b_{i,j}) \right] + (1 - p_i^{(a)})\ \mathcal{E}_{i+1}(\mathcal{B}). \tag{6.26}$$

Again, we note that Equation 6.26 has the same form as the Bellman Equation (as in Bellman (1957)). Given one is at state $\mathcal{B}$ at drug i, one may move to state $\mathcal{B}$ or $\mathcal{B} - b_{i,j}$ at drug $i+1$ given one chooses design j for drug i as illustrated in Figure 6-2.

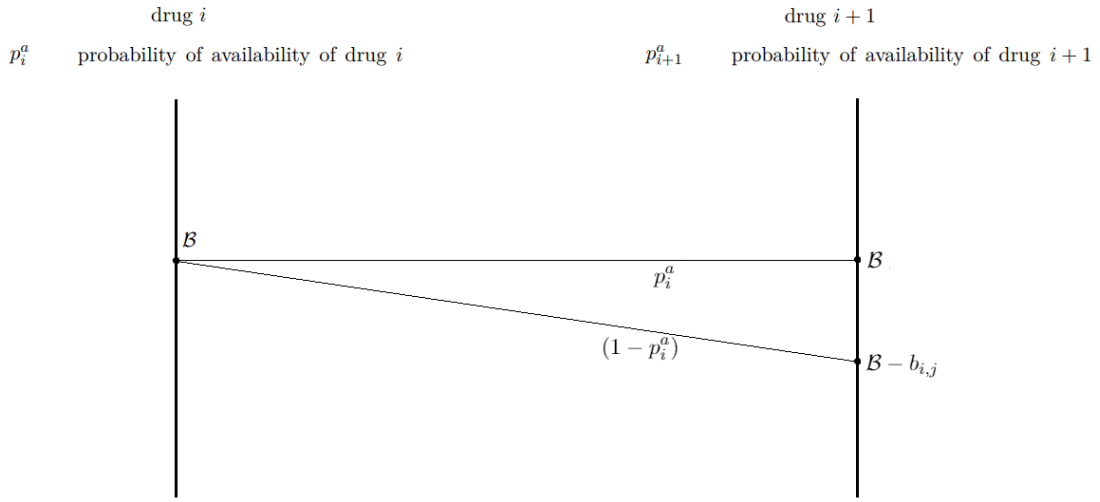

Figure 6-2: Figure showing the relationship between the state $\mathcal{B}$ at drug i and possible future states $\mathcal{B}'$ at drug $i+1$.

Dynamic Programming (Remaining Budget) Definition List

$\mathcal{B}$	State describing the remaining budget at some point in the portfolio.
$\mathcal{E}_i(\mathcal{B})$	Expected gain from drugs i to I given remaining budget $\mathcal{B}$ at drug i before allocation resources to drug i.
$\mathcal{J}_{i,\mathcal{B}}$	Possible designs one can afford at drug i with a remaining budget of $\mathcal{B}$.

Implementation

In this section we describe the algorithms to compute the optimal decisions in the portfolio as pseudo-code.

STEP 1: Gather inputs

- Portfolio inputs

$I,\ \alpha_i,\ J_i, \beta_{i,j},\ n_i^{\text{trials}},\ \mathcal{B}_{\text{PortTot}},\ \sigma_i^2,\ t_i^{(a)},\ p_i^{(a)},\ p_i^{\text{eff}},\ \mu_i^1,\ \mu_i^0$ for all appropriate i, j.

- Financial model inputs

$f_i,\ c_i,\ \lambda_i,\ t_{\text{trt}},\ F_i,\ t_i^s,\ T_i^p,\ \rho$ for all appropriate i.

STEP 2: Compute Designs

In this step, we use the financial model and portfolio inputs to calculate the budget and expected gain for each drug and design. As in the design history approach, we only consider fixed sample designs, so $b_{i,j}$ and $e_{i,j}$ are known a-priori for each drug i and design j.

- For each drug and design, calculate:
  - Budgets $b_{i,j}$ and expected gain $e_{i,j}$ for each $i = 1, ..., I$ and $j = 1, ..., J_i$ using the Financial Model equations of Section 6.1.

List the portfolio inputs in object $\mathfrak{I} := \{I,\ \mathcal{B}_{\text{PortTot}},\ (\mathfrak{I}_i)_{\{i=1,...,I\}}\}$, where
$\mathfrak{I}_i = \{p_i^{(a)}, (b_{i,j})_{\{j=1,...,J_i\}},\ (e_{i,j})_{\{j=1,...,J_i\}},\ n_i^{\text{trials}}\}$.

STEP 3: Initial Computations

For efficiency, remove designs that have higher budgets and lower expected gains than another design for the same drug.

The budget remaining part of the state space is a continuous quantity. However, we discretise it into a finite number of intervals. Let

$$\mathcal{B}_{\text{disc}} := \left\{ \frac{k-1}{N}\mathcal{B}_{\text{PortTot}} \ \middle|\ k = 1, 2, ..., N \right\} \tag{6.27}$$

be a set a budgets, each corresponding to an interval

$$\mathfrak{I}_k := \left[\frac{k-1}{N}\mathcal{B}_{\text{PortTot}} \ ,\ \frac{k}{N}\mathcal{B}_{\text{PortTot}} \right) \ \text{for } k = 1, ..., N. \tag{6.28}$$

A method for storing the optimal decisions and corresponding expected gain is to define a list `Opt_Dec_List`. This list is indexed by the drug i such that `Opt_Dec_List`$[[i]]$ is a dataframe detailing the optimal decisions for drug i. This dataframe consists of rows corresponding to the discrete intervals covering the Budget Remaining state space, with columns giving the optimal decisions and corresponding expected gain for the remainder of the portfolio for each interval. The optimal decision for each interval is found by finding the optimal decision for a sample within that interval (called a representative sample). To be conservative, one may choose this sample to be the lower bound of the interval.

In the algorithms below, we summarise the method used to calculate the optimal decisions for the portfolio.

STEP 4: Dynamic Programming Algorithm

```
Master_Function

Inputs: ℑ,Opt_Dec_List

for i in I,I − 1,...,1
        Opt_Dec_List ← Update_Opt_Decs(i,Opt_Dec_List)
end for loop
Return Opt_Dec_List
```

```
Update_Opt_Decs

Inputs: i,Opt_Dec_List

eG_vec ← Find_Opt_Decs(i, Opt_Dec_List)
Store eG_vec in a column in the dataframe Opt_Dec_List[[i]]
Return Opt_Dec_List
```

```
Find_Opt_Decs

Inputs: i,Opt_Dec_List

B_vec ← vector of representative samples of B, each from an interval in
Opt_Dec_List[[i]].
for each r_loop in 1, 2, ..., length(B_vec)
        Calculate the optimal design j* for remaining budget B_vec[r_loop]
        using Equation 6.26 with corresponding e_{i,j*}.
        This involves reading stored elements in Opt_Dec_List[[i + 1]].
        eG_vec[r_loop] ← e_{i,j*}
end for loop
Return eG_vec
```

6.4 A comparison of the different methods for the portfolio problem with fixed sample designs

In this section, we compare the computational efficiency of the three methods we have discussed so far when used to compute the optimal decisions of a portfolio consisting of fixed sample designs. We consider the stochastic integer programming method (SIP), the dynamic programming method with a design history state space (DP (History)), and the dynamic programming method with a remaining budget state space (DP (Remaining Budget)).

In Section 6.7, we shall examine different case studies. Therefore, we present results on the compuational efficiency for each of the methods for one of those examples.

Table 6.1: Computational time in seconds for computing the optimal decisions in a portfolio of drugs with fixed sample designs for the stochastic integer programming (SIP) and dynamic programming (DP) methods. The SIP method for 8 drugs does not complete within 2 hours (7200) seconds. All computations are run sequentially on a single core (Intel Core i7-7500U 2.7 GHz processor).

	Computational Time (seconds)		
	SIP	**DP (History)**	**DP (Remaining Budget)**
3 Drugs	6.15	0.30	1.01
4 Drugs	6.16	0.50	1.38
5 Drugs	5.98	0.64	2.94
6 Drugs	10.70	2.38	6.35
7 Drugs	13.23	12.09	11.96
8 Drugs	150.23	101.02	17.22
9 Drugs	-	979.10	21.71
25 Drugs	-	-	89.55

Table 6.1 shows the computational time for each method to find the optimal decision rules for the portfolio.

For portfolios with few drugs, the times taken for each method are fairly similar. As the number of drugs in the portfolio increases, the SIP and DP (History) method both take exponentially increasing times, since the number of possible design histories increases exponentially. The DP (Remaining Budget) increases at a linear rate with the addition of new drugs and therefore performs better for portfolios with large numbers of drugs.

For more complex portfolios, the DP (Remaining Budget) is the favoured method and we concentrate on this method for the remainder of this chapter. Only for smaller values of I is this method not the fastest, in which case there are few combinations of design histories. In Section 6.5, we generalise the DP (Remaining Budget) method to allow group sequential designs.

In Section 6.7.1 we shall look at the computational time for the DP (Remaining Budget) method for portfolios with an even larger number of drugs.

6.5 Generalisation of the dynamic programming (remaining budget) method to group sequential designs

In Chapter 2, we introduced group sequential designs and noted the benefit of using them within a Phase II/III programme. In a portfolio setting, group sequential designs can be advantageous in two ways. Firstly, stopping early will allow one to reinvest unused budgets back into the portfolio when the group sequential design stops. Secondly, stopping early for efficacy will allow one to market the drug for longer until the patent expires. In this section, we extend the dynamic programming (remaining budget) method to allow group sequential designs.

6.5.1 Method

Group sequential design situation ID

We suppose the group sequential trials for drug i each have K_i analyses.

The presence of group sequential designs in the portfolio complicates the state space as group sequential designs return leftover budget to the total portfolio budget if they stop before the final analysis. This means the optimal design for drug i is dependent on both the total remaining portfolio budget as before, and the current status of ongoing group sequential designs in the portfolio.

We therefore define an integer label s to be the GSD situation ID. This uniquely describes the current status of all the GSDs in the portfolio. That is, whether each group sequential design in the portfolio has terminated or was never started, if it is ongoing with a particular design, or if the availability time of the corresponding drug is in the future.

Dynamic programming *central equations*

The expected value of a decision in a portfolio with group sequential designs now not only depends upon the remaining budget, but on the current situation of the group sequential designs. For example, if one is making a design decision for a certain drug but a group sequential design for a previous drug is currently ongoing, then this group sequential design may terminate early at some point in the future, returning leftover budget. This may affect the optimal design decision at the current drug. In this subsection, we generalise the state space to keep track of both the current situation of all group sequential designs as well as the remaining portfolio budget.

Define the state $(\mathcal{B}, s)$ as the state of having remaining budget $\mathcal{B}$ and GSD situation ID s. Let $\mathcal{E}_i(\mathcal{B}, s)$ denote the sum of the expected value of the gain function from drugs i to I, given one is at state $(\mathcal{B}, s)$ at drug i.

The sample size realised for a group sequential design is a random variable. When performing the dynamic programming algorithm, we define $b_{i,j}$ as the maximum budget for drug i and design j. That is, we assume that the group sequential trial will run until its last analysis. This corresponds to the budget being 'locked away' until one knows one does not need the rest.

Given one is at state $(\mathcal{B}, s)$ at drug i, one may move to different states at drug $i+1$ due to the following two mechanisms:

- if drug i is available, choosing design j will reduce $\mathcal{B}$ by $b_{i,j}$, and
- if any ongoing GSDs terminate between drug i and $i+1$, s will change to reflect this, and leftover budget may be returned making $\mathcal{B}$ increase.

Recall the definition of $\mathcal{J}_{i,\mathcal{B}}$ from Section 6.3.2. For any state $(\mathcal{B}, s)$ and drug $i = 1, ..., I-1$ and design $j \in \mathcal{J}_{i,\mathcal{B}}$, we define

$$\mathcal{A}_{\mathcal{B},s,i,j} := \{(\mathcal{B}', s') \ : \ (\mathcal{B}', s') \text{ is a possible state at drug } i+1 \text{ given drug } i \text{ has design } j \text{ at state } (\mathcal{B}, s)\}.$$

This set gives the possible states one may move to at the next drug given the current state

at the current drug. For each new state $(\mathcal{B}', s')$ at drug $i+1$, one defines the probability of moving to it from $(\mathcal{B}, s)$ at drug i as $p_j^{(i)}((\mathcal{B}, s), (\mathcal{B}', s'))$, given drug i had design j. For fixed sample designs, this probability is 1 for $(\mathcal{B} - b_{i,j}, s)$ reflecting the budget used by using design j for drug i. For group sequential designs, these probabilities can be deduced from the probabilities $p_{\boldsymbol{n}_{i,j}}$ of observing a particular set of sample sizes as described in Section 6.1.

We now formulate the dynamic programming *central equations*.

$$\mathcal{E}_I(\mathcal{B}, s) = p_I^{(a)} \max_{j \in \mathcal{J}_{I,\mathcal{B}}} e_{I,j}, \tag{6.29}$$

and for $i = 1, ..., I-1$,

$$\begin{aligned}
\mathcal{E}_i(\mathcal{B}, s) &= p_i^{(a)} \max_{j \in \mathcal{J}_{i,\mathcal{B}}} \left[e_{i,j} + \sum_{(\mathcal{B}', s') \in \mathcal{A}_{\mathcal{B},s,j}} p_j^{(i)}((\mathcal{B}, s), (\mathcal{B}', s'))\ \mathcal{E}_{i+1}(\mathcal{B}', s')) \right] \\
&\qquad + (1 - p_i^{(a)}) \sum_{(\mathcal{B}', s') \in \mathcal{A}_{\mathcal{B},s,1}} p_1^{(i)}((\mathcal{B}, s), (\mathcal{B}', s'))\ \mathcal{E}_{i+1}(\mathcal{B}', s') \\
&= \max_{j \in \mathcal{J}_{i,\mathcal{B}}} \left[p_i^{(a)} e_{i,j} + \sum_{(\mathcal{B}', s') \in \mathcal{A}_{\mathcal{B},s,i,j} \cup \mathcal{A}_{\mathcal{B},s,i,1}} \left[p_i^{(a)}\ p_j^{(i)}((\mathcal{B}, s), (\mathcal{B}', s')) \right.\right. \\
&\qquad \left.\left. + (1 - p_i^{(a)})\ p_i^{(i)}((\mathcal{B}, s), (\mathcal{B}', s')) \right] \mathcal{E}_{i+1}(\mathcal{B}', s') \right].
\end{aligned} \tag{6.30}$$

As before, the key point of the *central equation* in Equation 6.30 is that the expected gain at state $(\mathcal{B}, s)$ at drug i may be written in terms of the sum of the expected gain at different states $(\mathcal{B}', s')$ at drug $i+1$, allowing for a dynamic programming approach.

In Figure 6-3, we show the relationship between a state at a particular drug and different states one may move to at the next drug.

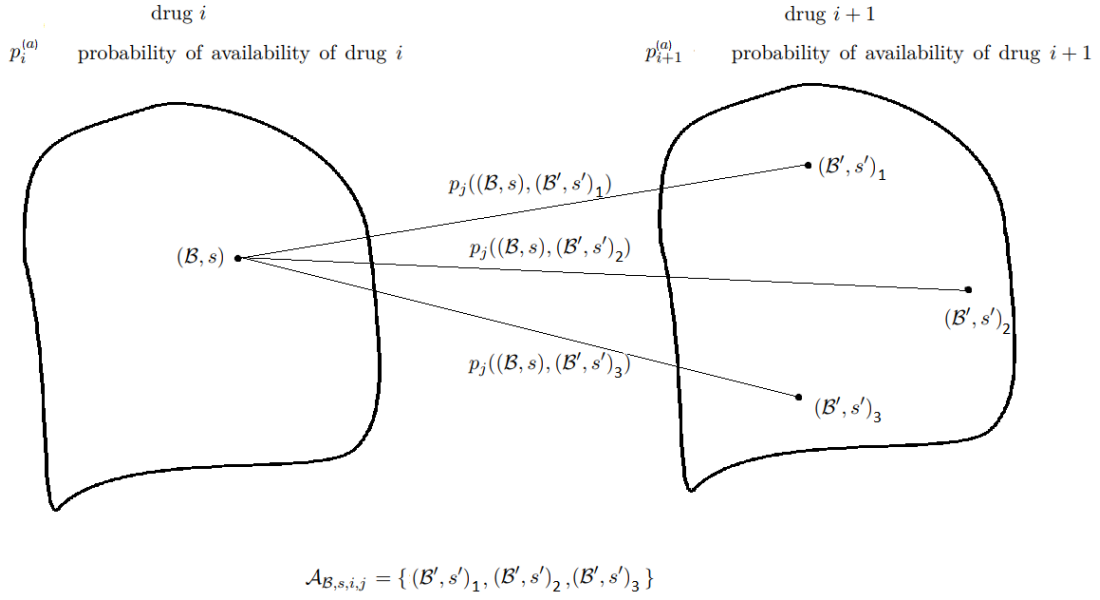

Figure 6-3: Figure showing the relationship between the state $(\mathcal{B}, s)$ at drug i and possible future states $(\mathcal{B}', s')$ at drug $i+1$, with corresponding probabilities given design j for drug i.

Dynamic Programming with GSDs (Remaining Budget) Definition List

$\mathcal{B}$	Remaining budget at some point in the portfolio.

s	Group sequential design ID at some point in the portfolio describing the current state of all the GSDs in the portfolio.
$(\mathcal{B}, s)$	State at a particular drug describing current values of $\mathcal{B}$ and s.
$\mathcal{E}_i(\mathcal{B}, s)$	Expected gain from drugs i to I given state $(\mathcal{B}, s)$ at drug i.
$\mathcal{A}_{\mathcal{B},s,i,j}$	Possible states at drug $i+1$ given state $(\mathcal{B}, s)$ at drug i and design j.
$p_j^{(i)}((\mathcal{B}, s), (\mathcal{B}', s'))$	Probability of moving to state $(\mathcal{B}', s')$ at drug $i+1$ given state $(\mathcal{B}, s)$ at drug i with design j. This includes what happens in all the continuing group sequential designs for drugs 1 to i.

Implementation

In this section we describe the algorithms to compute the optimal decisions in the portfolio as pseudo-code.

STEP 1: Gather inputs

- Portfolio inputs

$I,\ \alpha_i,\ J_i, \beta_{i,j},\ n_i^{\text{trials}},\ \mathcal{B}_{\text{PortTot}},\ \sigma_i^2,\ t_i^{(a)},\ p_i^{(a)},\ p_i^{\text{eff}},\ \mu_i^1,\ \mu_i^0$ for all appropriate i, j.

- Financial model inputs

$f_i,\ c_i,\ \lambda_i,\ t_{\text{trt}},\ F_i,\ t_i^s,\ T_i^p,\ \rho$ for all appropriate i.

STEP 2: Compute Designs

In this step, we use the financial model and portfolio inputs to calculate the budget and expected gain for each drug and design.

- Recall K_i is the number of analyses for group sequential designs for drug i. For drugs with GSDs, calculate the:
  - Analysis times $t_{i,j,k}^{\text{GSD}}$ and probabilities $p_{i,j,k}^{\text{GSD}}$ for each analysis $k = 1, ..., K_i$ for each group sequential trial $j = 1, ..., J_i$ for each drug $i = 1, ..., I$.
  - Budgets $b_{i,j}$ for each design $j = 1, ..., J_i$ and drug $i = 1, ..., I$, defined as $b_{i,j} := \max_{\boldsymbol{n}_{i,j}}(b_{i,j}^{(\boldsymbol{n}_{i,j})})$, the budget assuming all group sequential trials run until their final analysis using the notation from Section 6.1.
  - Expected gains $e_{i,j}$ for design $j = 1, ..., J_i$ for each drrug $i = 1, ..., I$.
- For drugs with fixed sample designs, calculate the:
  - Budgets $b_{i,j}$ and expected gain $e_{i,j}$ for each $i = 1, ..., I$ and $j = 1, ..., J_i$.

List the portfolio inputs in object $\mathfrak{I} := \{I,\ \mathcal{B}_{\text{PortTot}},\ (\mathfrak{I}_i)_{\{i=1,...,I\}}\}$, where

$$\mathfrak{I}_i = \{p_i^{(a)}, (b_{i,j})_{\{j=1,...,J_i\}},\ b_{i,j}^{(\boldsymbol{n}_{i,j})}{}_{\{j=1,...,J_i, \text{all possible } \boldsymbol{n}_{i,j}\}},\ (e_{i,j})_{\{j=1,...,J_i\}},\ t_i^{(a)},\ (t_{i,j,k}^{\text{GSD}})_{\{j=1,...,J_i,\ k=1,...,K_i\}},\ n_i^{\text{trials}}\}$$

.

STEP 3: Initial Computations

As before, we discretise the budget remaining $\mathcal{B}$ part of the state space.

As in the case with fixed sample designs in the previous sections, the method of Dynamic Programming is to work backwards, drug by drug, finding the optimal decisions for any possible state. This process works because the optimal decisions for a particular drug depend only on the current state, and the optimal decisions and corresponding expected gains for the next drug, as specified in Equation 6.26.

We discretise the Budget Remaining dimension of the state space into a finite number of intervals. A method for storing the optimal decisions and corresponding expected gain is to define a list `Opt_Dec_List`. This list is indexed by the drug i and GSD situation ID s such that `Opt_Dec_List`$[[i]][[s]]$ is a dataframe detailing the optimal decisions for drug i given a GSD situation ID s. This dataframe consists of rows corresponding to the discrete intervals covering the Budget Remaining state space, with columns giving the optimal decisions and corresponding expected gain for the remainder of the portfolio for each interval. The optimal decision for each interval is found by finding the optimal decision for a sample within that interval (called a representative sample). To be conservative, one may choose this sample to be close to the lower bound of the interval.

In the algorithms below, we summarise the method used to calculate the optimal decisions for the portfolio.

STEP 4: Dynamic Programming Algorithm

Master_Function

Inputs: $\mathfrak{I}$,`Opt_Dec_List`

for i in I,$I-1$,...,1
    `Opt_Dec_List` $\leftarrow$ *Update_Opt_Decs*(i,`Opt_Dec_List`)
end for loop
Return `Opt_Dec_List`

Update_Opt_Decs

Inputs: i,`Opt_Dec_List`

for each s possible for drug i
    `eG_vec` $\leftarrow$ *Find_Opt_Decs*(i, `Opt_Dec_List`, s)
    Store `eG_vec` in a column in the dataframe `Opt_Dec_List`$[[i]][[s]]$
end for loop
Return `Opt_Dec_List`

Find_Opt_Decs

Inputs: i,`Opt_Dec_List`,s

$\mathcal{B}$`_vec` $\leftarrow$ vector of representative samples of $\mathcal{B}$, each from an interval in `Opt_Dec_List`$[[i]][[s]]$.
for each r_{loop} in $1, 2, ...,$ length($\mathcal{B}$`_vec`)
    Calculate the optimal design j^* for remaining budget $\mathcal{B}$`_vec`$[r_{\text{loop}}]$
    using Equation 6.30 with corresponding e_{i,j^*}.
    This involves reading stored elements in `Opt_Dec_List`$[[i+1]][[s']]$ for
    different possible s'.
    `eG_vec[r_loop]` $\leftarrow$ e_{i,j^*}
end for loop
Return `eG_vec`

An illustrative example

To illustrate the subtleties arising from the calculation of optimal decisions involving portfolios with group sequential designs, we give an illustrative example. For simplicity, we describe the budgets, expected gains, and the lengths of each design of each drug directly in the table below and displayed in Figure 6-4.

	Drug 1	Drug 2
$t_i^{(a)}$	1	4
$p_i^{(a)}$	1	0.5
n_i^{trials}	2	2
Design 1 type	GSD, $K_1 = 2$	GSD, $K_2 = 2$
Design 1 budget	1 per analysis per trial	1 per analysis per trial
Design 1 eGain	$e_{1,1} = 2$	$e_{2,1} = 2$
Design 2 type	n/a	GSD, $K_2 = 2$
Design 2 budget	n/a	total per trial: first analysis: 2, second: 3
Design 2 eGain	n/a	$e_{2,2} = 3$

We suppose the budget for the portfolio is 8 units and that all group sequential designs take 1 time unit per analysis with a probability of 0.5 of stopping at each of the first and second analyses.

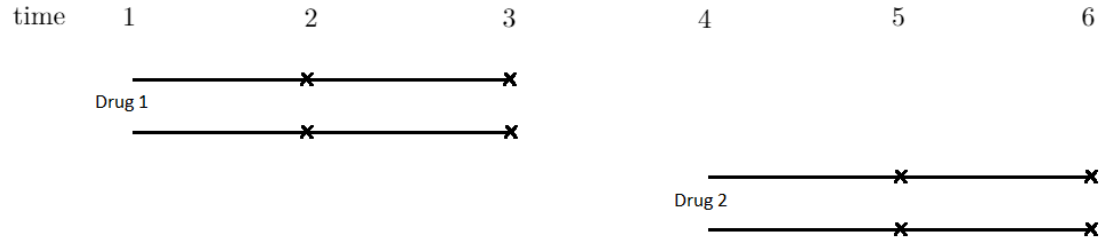

Figure 6-4: A schematic of the two drugs with group sequential designs in the illustrative example.

Consider the situation at time point 4 given Drug 1 was run with 2 group sequential trials. Each group sequential trial for Drug 1 may have stopped at the first analysis or the second. Therefore, the remaining budget will be $8-2\times 2=4$, $8-2-1=5$, or $8-2\times 1=6$. In the case when the remaining budget is 6, one may choose design 2 for Drug 2 if it is available which has a maximum budget of $2\times 3=6$. Otherwise, one must choose design 1 for Drug 2 if it is available which has a maximum budget of $2\times 2=4$.

Therefore, one may work out the expected gain of the portfolio by conditioning firstly on whether Drug 2 is available (with probability 0.5) or not (with probability 0.5), and secondly whether the remaining budget is 6 (with probability 0.25) or less than 6 (with probability 0.75).

$$\begin{aligned}\text{expected gain of portfolio} &= 2+0.5\times(0.25\times 3+0.75\times 2)+0.5\times 0\\ &= 3.125\end{aligned} \tag{6.31}$$

Using the dynamic programming algorithm, we obtain the same portfolio expected gain of 3.125. The optimal decisions may be listed in the following format.

Drug 1 Optimal Decisions					Drug 2 Optimal Decisions, $s=1$				
Int Start	Int End	j^*	b_{1,j^*}	e_{1,j^*}	Int Start	Int End	j^*	b_{2,j^*}	e_{2,j^*}
8	8	1	4	2	0	4	none	0	0
					4	6	1	4	2
					6	8	2	6	3

The interval start (Int Start) and end (Int End) give the intervals of total remaining portfolio budget in which one has the same optimal decision for each drug. At Drug 1, we know the total portfolio budget is 8. At Drug 2, we only consider the states with $s=1$ because by the time Drug 2 is available, all of the group sequential designs from Drug 1 have terminated. For each interval (row), we have the optimal design j^*, the maximum budget b_{i,j^*}, and expected gain e_{i,j^*} for $i=1,2$.

6.6 Quantifying the variability in achieved gain associated with optimal design strategy

Suppose the optimal decision rules for all states and drugs have been computed. The expected gain of the optimal decision at the initial state at Drug 1 represents the expected gain of the entire portfolio under this strategy. One may refer to this quantity as the *expected value* of the portfolio.

The portfolio by design has a stochastic nature due to the uncertainty as to the availability of drugs, whether each drug has a successful Phase III, the times at which GSDs end, and the revenue per month of a marketed drug. For example, if fewer drugs are available than expected, one may obtain a gain less than expected, and if more drugs are available than expected, one may obtain a gain higher than expected. Understanding the risk associated with investing in the portfolio is as important as understanding the expected return.

In this section, we describe how to obtain the distribution of the gain, given one follows the optimal decision rules. We use a Monte Carlo approach as motivated by Patel et al. (2013),

simulating runs of the portfolio. In each simulation, the stochastic elements of the portfolio, such as the availability of each drug, are sampled. We specify the Monte Carlo algorithm below.

```
Simulation_Function

Simulate the revenue per month of each drug.
for i in 1,2,...,I − 1,I
        Simulate whether drug i is available.
        If available, look up optimal design given remaining budget and
        simulate whether Phase III is successful and R_i and store the
        corresponding gain.
        If design is group sequential, also simulate analysis of termination.
        If before final analysis, store leftover budget to be added to
        remaining portfolio budget at the appropriate time.
        Updated remaining portfolio budget.
end for loop
Return the sum of the gains from drugs 1, 2, ..., I.
```

Suppose one runs N Monte Carlo simulations of the portfolio using the above algorithm. The set of portfolio gains can be used to approximate the distribution of the gain under the optimal decision rules. Furthermore, the distribution of the decision for each drug, and the distribution of the total portfolio budget used are found.

6.7 Case studies

In this section we consider five case studies and apply our dynamic programming method to find the optimal decision rules. The first case study aims to model a realistic scenario in portfolio decision making where the portfolio consists of 7 drugs with fixed sample designs. The other case studies make changes to the portfolio scenario to show the flexibility of this approach to make inferences about different situations, such as when one uses group sequential designs or when there are competitor drugs being developed.

6.7.1 Case Study 1: A portfolio of 7 drugs

Case Study 1 aims to model a realistic portfolio with 7 drugs with fixed sample designs. In this section, we specify the inputs used in the model, and then describe the results of the dynamic programming with a remaining budget state space algorithm including the expected portfolio gain, the optimal decisions, and the associated risk. The inputs are taken from the paper of Patel et al. (2013) and are displayed in Table 6.2.

Inputs

Total portfolio budget: 150. In Table 6.2, we list the other inputs for Case Study 1.

Results

In Tables 6.3 and 6.4, we list the budgets required and expected gains for each drug i and design j. Recall design $j = 1$ with a sample size of 0 represents no Phase III trial occuring.

Table 6.2: Inputs for Case Study 1

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
$t_i^{(a)}$	1	1	3	6	13	18	25
$p_i^{(a)}$	1	1	0.1	0.1	0.1	0.9	0.1
p_i^{eff}	0.5	0.5	0.5	0.5	0.5	0.5	0.5
α_i	0.05	0.05	0.05	0.05	0.05	0.05	0.05
σ_i	2	1.8	2	2	1.5	1.5	1
λ_i	20	30	90	45	60	90	45
c_i	11.09	16.64	25.29	23.63	25.79	14.84	14.01
f_i	2805	15	525	2125	240	125	500
T_i^P	108	120	135	180	155	180	145
t_i^s	6.3	7	18	18	30	12	18
F_i	50000	500000	400000	300000	500000	300000	1000000
R_i^{mean}	175000	85000	400000	200000	45000	250000	500000
R_i^{sd}	35000	17000	80000	40000	9000	50000	100000
μ_1	0.5	0.4	0.5	0.4	0.4	0.3	0.25
μ_0	0	0	0	0	0	0	0
t_{trt}	0.3	1	12	12	24	6	12
n_i^{trials}	2	2	2	2	2	2	2
ρ	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083
$1-\beta_{i,1}$	0	0	0	0	0	0	0
$1-\beta_{i,2}$	0.80	0.80	0.80	0.80	0.80	0.80	0.80
$1-\beta_{i,3}$	0.85	0.85	0.85	0.85	0.85	0.85	0.85
$1-\beta_{i,4}$	0.90	0.90	0.90	0.90	0.90	0.90	0.90
$1-\beta_{i,5}$	0.95	0.95	0.95	0.95	0.95	0.95	0.95
$1-\beta_{i,6}$	0.99	0.99	0.99	0.99	0.99	0.99	0.99

Table 6.3: The budgets $b_{i,j}$ for each drug i and design j to 3 significant figures ($M).

	Design 1	*Design 2*	*Design 3*	*Design 4*	*Design 5*	*Design 6*
Drug 1	0	14.4	15.8	17.8	21.0	28.0
Drug 2	0	16.7	19.4	23.1	29.2	42.6
Drug 3	0	21.1	24.3	28.8	36.1	52.1
Drug 4	0	33.5	38.2	44.7	55.4	78.7
Drug 5	0	18.4	21.3	25.3	31.9	46.2
Drug 6	0	18.6	21.6	25.7	32.4	47.1
Drug 7	0	12.1	13.9	16.4	20.4	29.3

Table 6.4: The expected gain $e_{i,j}$ for each drug i and design j from the financial model gain function, to 3 significant figures ($M).

	Design 1	*Design 2*	*Design 3*	*Design 4*	*Design 5*	*Design 6*
Drug 1	0	2644	2823	2925	2840	2178
Drug 2	0	1308	1411	1486	1485	1237
Drug 3	0	6249	6975	7701	8366	8587
Drug 4	0	3311	3630	3910	4071	3785
Drug 5	0	347	384	418	442	424
Drug 6	0	4558	5072	5576	6017	6083
Drug 7	0	5434	5982	6477	6808	6463

After running the dynamic programming algorithm, the portfolio value can be summarised as

Portfolio Expected Gain	11 834
Standard Deviation	*9 325*,

with individual drug contributions from simulation found as

	Drug						
	1	2	3	4	5	6	7
Expected Gain ($M)	*2925*	*1486*	*861*	*395*	*36*	*5461*	*667*

In Table 6.7.1, we list the optimal designs for each drug given the portfolio budget remaining. Note that we only consider states which are possible- for example, a portfolio budget remaining of less than 122.0 is not possible for Drug 2 as the largest budget for Drug 1 is 28.0, so one cannot have less than 150.0-28.0=122.0.

Figure 6-5 displays the optimal decision plots for each drug using the data in Table 6.7.1. From these optimal decision plots, one can see it is important to have at least 18.6M\$ budget remaining for Drug 6, which has a high probability of availability (0.9) and a substantial expected gain. For some drugs and budgets, it is better to choose Design 1 (that is, no Phase III trial) even if the drug is available, in order to save the budget for drugs with larger rewards later on in the portfolio. Often over short intervals of the budget, the optimal decisions may change frequently.

In Figure 6-5, we have plotted the optimal decisions for all drugs and remaining budgets between 0M\$ and 150M\$. If one is only interested in the value of the portfolio and the optimal decision rules, then for efficiency, one only has to calculate the optimal decision for Drug 1 with remaining budget of 150M\$ and only possible remaining budgets for Drugs 2-7.

Table 6.5: For each drug, the optimal decision given the total remaining portfolio budget. Each row is an interval (Int Start, Int End) on the budget remaining state space, with j^* the optimal decision, and b_{i,j^*} and e_{i,j^*} the corresponding budgets and expected gains.

Drug 1 Optimal Decisions

Int Start	Int End	j^*	b_{1,j^*}	e_{1,j^*}
150.0	150.0	4	17.8	2924.9

Drug 2 Optimal Decisions

Int Start	Int End	j^*	b_{2,j^*}	e_{2,j^*}
122.0	150.0	4	23.12	1485.5

Drug 3 Optimal Decisions

Int Start	Int End	j^*	b_{3,j^*}	e_{3,j^*}
98.9	104.9	5	36.1	8365.6
104.9	106.5	6	52.1	8586.6
106.5	107.2	5	36.1	8365.6
107.2	150.0	6	52.1	8586.6

Drug 4 Optimal Decisions

Int Start	Int End	j^*	b_{4,j^*}	e_{4,j^*}
46.8	52.1	1	0	0
52.1	63.9	2	33.5	3311.0
63.9	65.9	3	38.2	3630.5
65.9	70.4	2	33.5	3311.0
70.4	70.6	4	44.7	3909.5
70.6	77.1	3	38.2	3630.5
77.1	82.7	4	44.7	3909.5
82.7	89.2	3	38.2	3630.5
89.2	99.9	4	44.7	3909.5
99.9	150.0	5	55.4	4071.2

Drug 5 Optimal Decisions

Int Start	Int End	j^*	b_{5,j^*}	e_{5,j^*}
0	62.9	1	0	0
62.9	70.1	2	18.4	347.3
70.1	74.1	3	21.3	384.0
74.1	84.7	4	25.3	418.0
84.7	88.8	5	31.9	442.3
88.8	99.4	4	25.3	418.0
99.4	150.0	5	31.9	442.3

Drug 6 Optimal Decisions

Int Start	Int End	j^*	b_{6,j^*}	e_{6,j^*}
0	18.6	1	0	0
18.6	21.6	2	18.6	4557.6
21.6	25.7	3	21.6	5072.0
25.7	32.4	4	25.7	5576.5
32.4	37.8	5	32.4	6016.7
37.8	44.5	4	25.7	5576.5
44.5	63.4	5	32.4	6016.7
63.4	150.0	6	47.1	6082.5

Drug 7 Optimal Decisions

Int Start	Int End	j^*	b_{7,j^*}	e_{7,j^*}
0	12.1	1	0	0
12.1	13.9	2	12.1	5433.8
13.9	16.4	3	13.9	5981.5
16.4	20.4	4	16.4	6476.7
20.4	150.0	5	20.4	6807.5

Figure 6-6 shows the distribution of the final gain that is realised given all the stochastic elements inherent in the model. This includes the uncertainty attached to the return per month from marketing the drug. The distribution is smooth due to the large combinations of different revenues and costs that may be incurred such as having different revenues per month. There is a peak of density of NPV around 0 representing no drugs being successful in the portfolio (due to lack of availability or failure in Phase III), with a peak around 3000 representing a single success.

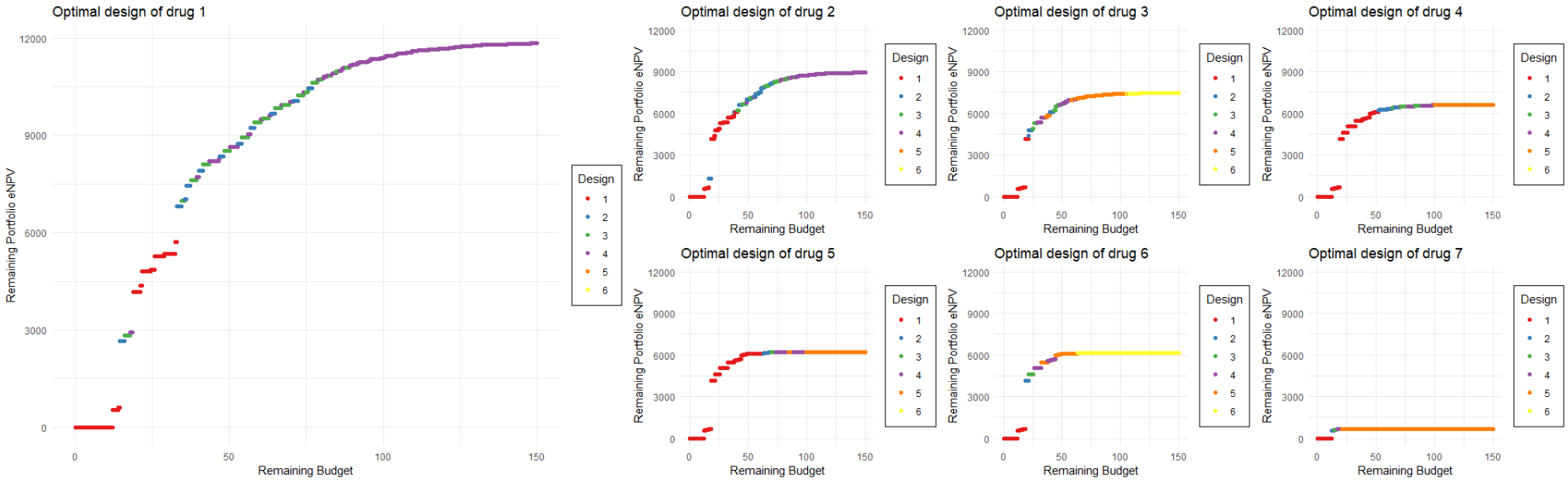

Figure 6-5: The optimal decisions for each drug. For each drug and portfolio remaining budget, each plot gives the optimal design for the drug (given by the colour) and the expected gain of the rest of the portfolio including the current drug.

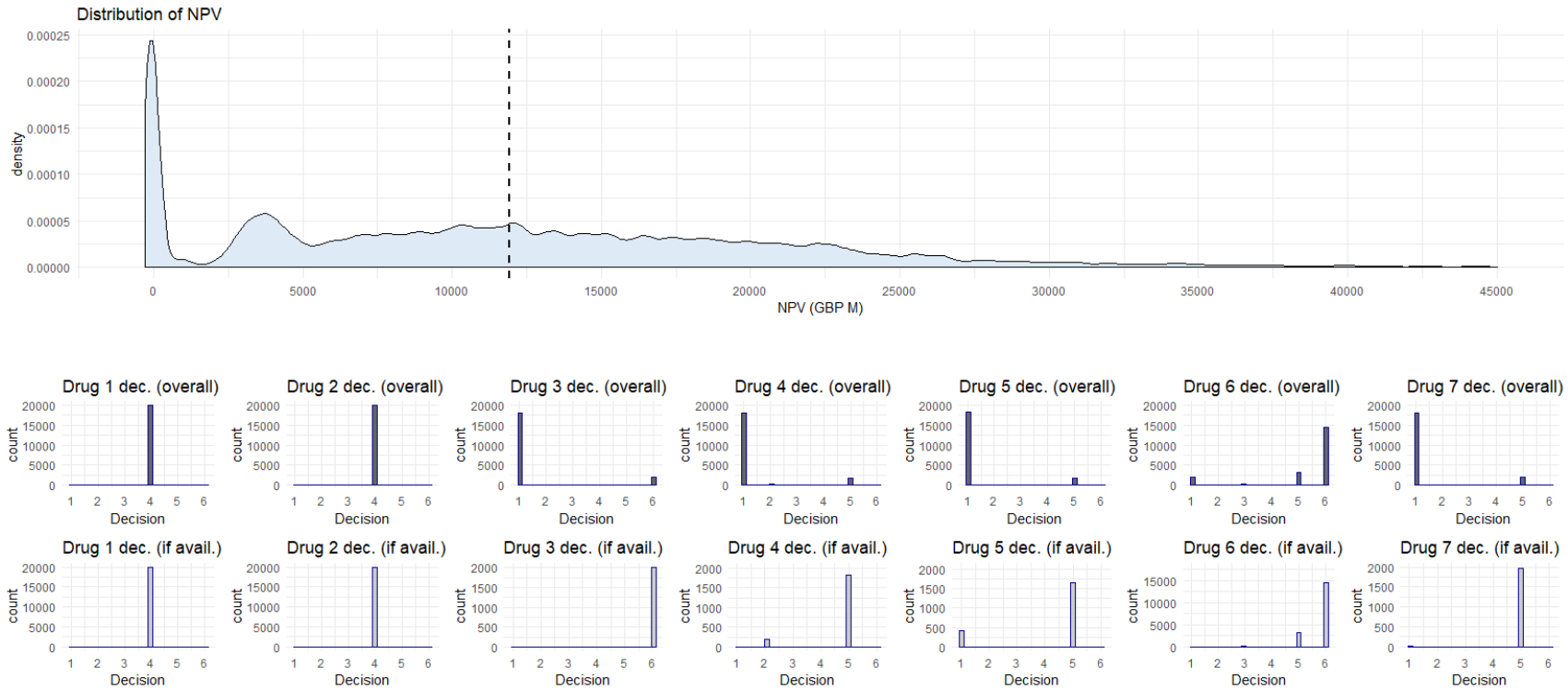

Figure 6-6: (Top) The distribution of the expected gain of the portfolio, given as a density plot using the simulation method described in Section 6.6. (Bottom) The histograms show distribution of the designs chosen given one follows the optimal decisions.

Portfolio expected gain as a function of portfolio budget

In this section we consider whether the budget for the portfolio of 150M$ is large enough. We can answer this by looking at the portfolio expected gain for different portfolio budgets. To do this, we examine the first plot in Figure 6-5.

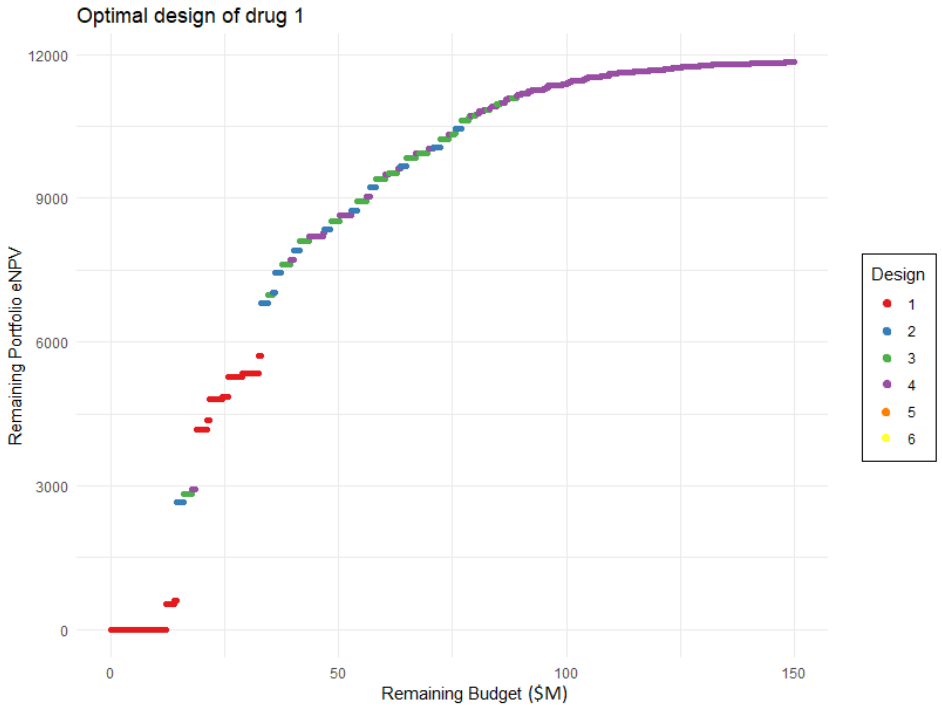

Figure 6-7: The portfolio expected gain and optimal decision for Drug 1, for any total portfolio budget, taken from Figure 6.7.4.

From this figure, one may deduce an investment of at least 100M$ is needed for most of the benefit to be obtained from this portfolio. Investment beyond this amount yields a lower return per extra unit of budget available. The total budget one may possibly consume if one chose the design for each drug with the highest budget would be 323M$ which is far higher than needed to obtain most of the value of the portfolio. This is because it is unlikely all drugs will be available and the most expensive design may not always have the highest expected gain due to a larger number of patients taking longer to test meaning there is a shorter time to market the drug until patent expiry.

The value of making optimal decisions

In this case study we have assumed one makes decisions optimally. That is, one chooses the design for each drug based on which design maximises the expected gain for the remainder of the portfolio when one follows optimal decision rules for the remainder of the portfolio. It may be useful to know how much better this decision making strategy is compared to common industrial practises. Thus in this section, we compare making decisions optimally with some other decision-making strategies.

We use the same portfolio parameters and inputs as before whilst varying the total portfolio budget $\mathcal{B}_{\text{PortTot}}$. We examine to what extent changing the way one makes decisions in the portfolio reduces the expected gain of the portfolio, and do this for a variety of total portfolio

budgets. Below, we define 5 decision making strategies:

Decision Rule Name	**Description**
Optimal	Choose $j^* \in \mathcal{J}_{i,\mathcal{B}}$ such that $\mathcal{E}_i(\mathcal{B}, s)$ is maximised.
Constrained EG current drug	Choose $j^* \in \mathcal{J}_{i,\mathcal{B}}$ such that $e_{i,j}$ is maximised among j s.t. $e_{i,j}/b_{i,j} > c$ for some $c > 0$ ($j^* = 1$ if there is no such j).
EG current drug	Choose $j^* \in \mathcal{J}_{i,\mathcal{B}}$ such that $e_{i,j}$ is maximised.
Unconstrained RR	Choose $j^* \in \mathcal{J}_{i,\mathcal{B}} \setminus \{1\}$ such that $e_{i,j}/b_{i,j}$ is maximised if $\mathcal{J}_{i,\mathcal{B}} \neq \{1\}$. Otherwise choose $j^* = 1$.
At random	Choose j^* from $\mathcal{J}_{i,\mathcal{B}}$ at random.

For the *Constrained EG current drug* decision rule, one assumes trial managers know which return ratio is particularly worthwhile investing in for their therapeutic area, so we optimise the value of c for each portfolio budget for a fair comparison. This optimisation was done by performing a bisection search for the value of c that maximises the portfolio expected gain which is calculated using simulation over 10,000 portfolio realisations.

In the table below, we display the portfolio expected gain and standard deviation for portfolios with the different decision rules. We then repeat this for different portfolio budgets.

	$\mathcal{B}_{\text{PortTot}}$=150	
Decision Rule	**Portfolio expected gain**	**Portfolio gain sd**
Optimal	11 834	2 095
Constrained EG current drug	11 683	2 114
EG current drug	11 683	1 998
Unconstrained RR	9 726	2 047
Random	8 639	2 115

	$\mathcal{B}_{\text{PortTot}}$=100	
Decision Rule	**Portfolio expected gain**	**Portfolio gain sd**
Optimal	11 375	2 112
Constrained EG current drug	10 834	2 124
EG current drug	10 124	2 010
Unconstrained RR	9 638	2 076
Random	6 677	1 899

	$\mathcal{B}_{\text{PortTot}}$=60	
Decision Rule	**Portfolio expected gain**	**Portfolio gain sd**
Optimal	9 407	2 057
Constrained EG current drug	8 696	2 323
EG current drug	8 195	2 013
Unconstrained RR	7 986	2 104
Random	4 886	2 013

One can see that for all portfolio budgets, the portfolio expected gain suffers when decisions are not made optimally. However, the *Constrained EG current drug* and *EG current drug* decision rules are not a great deal worse than the optimal decision rule. However, as the portfolio budget decreases, the difference between the optimal and non-optimal decision rules widen.

As one can see from Figure 6-8, the *expected gain from current drug* decision rule is disadvantaged by picking larger designs earlier on, and not having enough budget left to pick large designs for later more profitable drugs (in particular, Drug 6). In particular, the *Optimal* decision rule chooses Designs 3 and 2 for Drugs 1 and 2 compared to 4 and 4 when using the *EG current drug* decision rule- however at Drug 6, the *Optimal* decision rule may choose Design 4 whilst the *EG current drug* decision rule chooses Design 2. The lack of foresight in this decision rule comes at a cost to the overall portfolio value and therefore this example shows the benefit of fully optimal decision rules. The *Constrained EG current drug* goes some way to alleviating this problem, but is still inferior to the optimal decision rule.

If the total budget is very large, there is no need to worry about leaving budget for other drugs later on, so the *expected gain from current drug* decision rule will be close to *Optimal*. With a smaller total budget, it makes sense to consider the opportunity cost of spending heavily at the start of the portfolio which the *Optimal* decision rule accounts for.

Efficiency for portfolios with large numbers of drugs

A motivation for the dynamic programming with a budget remaining state space approach was its computational efficiency compared to other methods. Here, we evaluate the computational expense required to compute the optimal decisions of portfolios with a large number of drugs, where other methods would not be sufficient (as shown in Section 6.4).

Let *Comp Time 1* be the time in seconds to perform the dynamic programming algorithm sequentially, and *Comp Time 2* be the same time when done in parallel with 4 cores with an Intel Core i7-7500U 2.7 GHz processor. The r_{loop} loop in the algorithms in Section 6.5.1 can be done in parallel.

From Table 6.6, we see although parallel is initially slower for fewer drugs, for a larger number of drugs it is faster than sequential. As the number of drugs becomes very large (25), the computational times are still of the order of minutes.

This simulation study shows that using parallel computing does not increase the efficiency of the algorithm by a large amount. When group sequential designs are included, and each stage of the dynamic programming algorithm becomes a much lengthier calculation, parallel computing will reduce the computational time required.

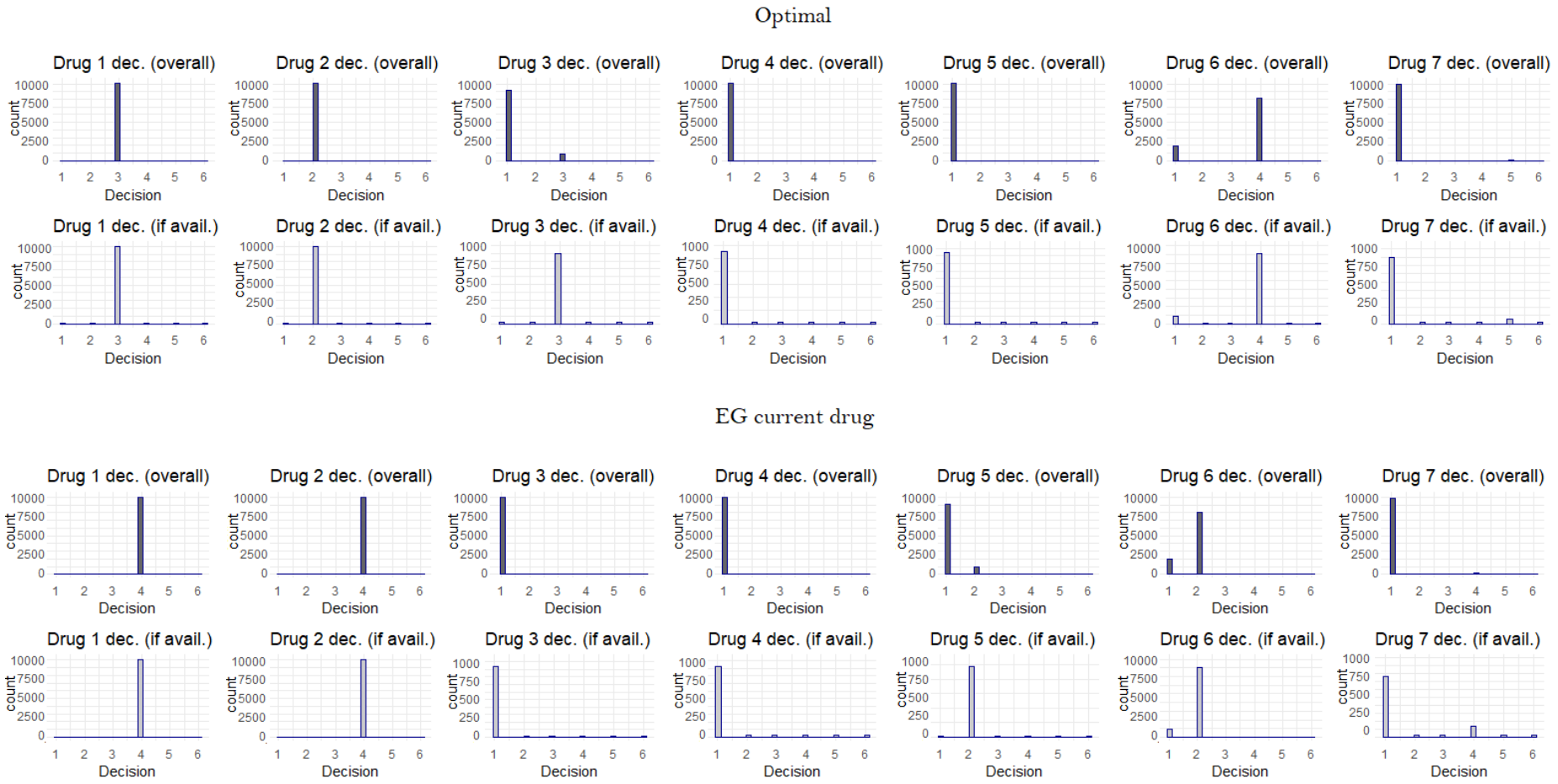

Figure 6-8: Decision made following each decision rule from simulations of 10000 portfolio realisations when following the (top) *Optimal* and (bottom) *EG current drug* decision rules when B_{PortTot}=100. Note that *overall* refers to simulations in which the corresponding drug was and was not available, whilst *if avail.* refers to simulations only in which the corresponding drug was available.

Table 6.6: The time taken in seconds for the dynamic programming algorithm to find the optimal decisions of the portfolio.

# Drugs	Comp Time 1	Comp Time 2	# Drugs	Comp Time 1	Comp Time 2
3	1.01	2.62	10	25.88	21.07
4	1.38	3.94	11	27.53	23.15
5	2.94	3.89	12	31.58	26.19
6	6.35	8.49	14	42.33	33.08
7	11.96	11.54	16	54.4	41.18
8	17.22	15.24	20	59.88	52.37
9	21.71	18.42	25	89.55	66.52

6.7.2 Case Study 2: Introducing group sequential designs

In this case study, we examine the value of group sequential designs (GSDs) in a portfolio. We consider the same inputs as the first case study but allow two drugs to have GSDs.

In particular, the portfolio inputs from Case Study 1 are used but with Drug 1 and 6 having Pampallona-Tsiatis GSDs as outlined in Pampallona and Tsiatis (1994) with $\Delta = 0.5$ and 5 analyses.

Inputs

Total portfolio budget: 150M$. We display the rest of the portfolio inputs in Table 6.7.

The GSD identifier s

Central to the dynamic programming algorithm is the reduction of current situation of all the GSDs in the portfolio to an integer identifier, the GSD situation ID, as outlined in Section 6.5.1. The parameter s takes integer values, each of which corresponds to a current state of the group sequential designs in the portfolio with $s = 1$ corresponding to there being no currently ongoing group sequential trials. In this case study, there are 4 group sequential trials, 2 each for Drugs 1 and 6. Not all values of s may be possible at each drug, so the algorithm only computes optimal decisions for possbile values of s. In particular, the only possible value of s at Drug 1 is $s = 1$.

Table 6.7: Inputs for Case Study 2

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
a_i	1	1	3	6	13	18	25
$p_i^{(a)}$	1	1	0.1	0.1	0.1	0.9	0.1
p_i^{eff}	0.5	0.5	0.5	0.5	0.5	0.5	0.5
α_i	0.05	0.05	0.05	0.05	0.05	0.05	0.05
σ_i	2	1.8	2	2	1.5	1.5	1
λ_i	20	30	90	45	60	90	45
c_i	11.09	16.64	25.29	23.63	25.79	14.84	14.01
f_i	2805	15	525	2125	240	125	500
T_i^P	108	120	135	180	155	180	145
t_i^s	6.3	7	18	18	30	12	18
F_i	50000	500000	400000	300000	500000	300000	1000000
R_i^{mean}	175000	85000	400000	200000	45000	250000	500000
R_i^{sd}	35000	17000	80000	40000	9000	50000	100000
μ_1	0.5	0.4	0.5	0.4	0.4	0.3	0.25
μ_0	0	0	0	0	0	0	0
t_{trt}	0.3	1	12	12	24	6	12
n_i^{trials}	2	2	2	2	2	2	2
ρ	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083
GSD?	Yes	No	No	No	No	Yes	No
GSD Type	TS $\Delta = .5$					TS $\Delta = .5$	
GSD # Analyses	5					5	
$1 - \beta_{i,1}$	0	0	0	0	0	0	0
$1 - \beta_{i,2}$	0.80	0.80	0.80	0.80	0.80	0.80	0.80
$1 - \beta_{i,3}$	0.85	0.85	0.85	0.85	0.85	0.85	0.85
$1 - \beta_{i,4}$	0.90	0.90	0.90	0.90	0.90	0.90	0.90
$1 - \beta_{i,5}$	0.95	0.95	0.95	0.95	0.95	0.95	0.95
$1 - \beta_{i,6}$	0.99	0.99	0.99	0.99	0.99	0.99	0.99

Results

Below, we list the expected gain, NPV, and probabilities split by analysis and design, for a single GSD for Drug 1.

Table 6.8: The Drug 1 cost per group sequential design for drug $i = 1$ dependent on the design j and the group sequential analysis the trial stops at.

Analysis	*Design 1*	*Design 2*	*Design 3*	*Design 4*	*Design 5*	*Design 6*
Analysis 1	0	5.78	5.96	6.22	6.62	7.47
Analysis 2	0	7.34	7.72	8.24	9.05	10.74
Analysis 3	0	8.91	9.49	10.25	11.47	14.00
Analysis 4	0	10.47	11.25	12.27	13.89	17.27
Analysis 5	0	12.04	13.01	14.29	16.31	20.54

Table 6.9: The Drug 1 revenue given both trials are successful terminate at a particular analysis.

Analysis	*Design 1*	*Design 2*	*Design 3*	*Design 4*	*Design 5*	*Design 6*
Analysis 1	0	10149	10013	9835	9557	8991
Analysis 2	0	9078	8824	8492	7981	6962
Analysis 3	0	8069	7710	7247	6541	5168
Analysis 4	0	7117	6668	6093	5227	3581
Analysis 5	0	6220	5693	5023	4027	2178

Table 6.10: The probabilities in each GSD for Drug 1 of terminating at a particular analysis with specified event, given the design chosen. *GO* refers to stopping for efficacy and *NOGO* refers to stopping for futility.

	Design 1	*Design 2*	*Design 3*	*Design 4*	*Design 5*	*Design 6*
Analysis 1 GO	n/a	0.158	0.171	0.190	0.217	0.271
Analysis 2 GO	n/a	0.140	0.149	0.158	0.166	0.167
Analysis 3 GO	n/a	0.083	0.085	0.085	0.080	0.060
Analysis 4 GO	n/a	0.036	0.036	0.035	0.030	0.018
Analysis 5 GO	n/a	0.009	0.009	0.008	0.007	0.004
Analysis 1 NOGO	n/a	0.336	0.303	0.265	0.217	0.144
Analysis 2 NOGO	n/a	0.148	0.152	0.157	0.166	0.181
Analysis 3 NOGO	n/a	0.062	0.065	0.071	0.080	0.105
Analysis 4 NOGO	n/a	0.023	0.024	0.026	0.030	0.040
Analysis 5 NOGO	n/a	0.006	0.006	0.006	0.007	0.010

After running the dynamic programming algorithm, one may observe the portfolio value increases from 11 834 in Case Study 1:

Expected Gain	12 654
Standard Deviation	*9 782.*

with individual drug contributions found from simulation as

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
Expected Gain Case Study 1	*2925*	*1486*	*861*	*395*	*36*	*5461*	*667*
Expected Gain Case Study 2	*3378*	*1486*	*831*	*337*	*31*	*5885*	*643*

In Table 6.11 we list some of the optimal decision rules as in Case Study 1. In this case study, the optimal decisions depend upon the remaining portfolio budget and GSD situation ID s. Therefore we only list the optimal decision rules for a selection of s values below.

In Figures 6-9 and 6-10, we present the optimal designs for each drug in the case when $s = 1$ (no ongoing GSDs), and show the distribution of the gain of the portfolio. Figure 6-11 gives the distribution of programme sample size from simulations of the portfolio with the optimal decision rules and compares it to Case Study 1.

Table 6.11: Optimal decision rules for Case Study 2

Drug 1 Optimal Decisions

Int Start	Int End	j^*	b_{1,j^*}	e_{1,j^*}
150.0	150.0	5	26.9	3376.4

Drug 2, Optimal Decisions for $s = 1, ..., 13$

Int Start	Int End	j^*	b_{2,j^*}	e_{2,j^*}
116.0	150.0	4	23.12	1485.5

Drug 3, Optimal Decisions for $s = 1, ..., 8, 10, 12$

Int Start	Int End	j^*	b_{3,j^*}	e_{3,j^*}
92.9	118.2	5	36.082	8365.6
118.2	150.0	6	52.1	8586.6

Drug 3, Optimal Decisions for $s = 9$

Int Start	Int End	j^*	b_{3,j^*}	e_{3,j^*}
92.9	114.3	5	36.082	8365.6
114.3	150.0	6	52.1	8586.6

Drug 3, Optimal Decisions for $s = 11$

Int Start	Int End	j^*	b_{3,j^*}	e_{3,j^*}
92.9	113.7	5	36.082	8365.6
113.7	150.0	6	52.1	8586.6

Drug 4, Optimal Decisions for $s = 1$

Int Start	Int End	j^*	b_{4,j^*}	e_{4,j^*}
40.8	58.5	1	0	0
58.5	70.6	2	33.5	3311.0
70.6	72.6	3	38.2	3630.5
72.6	77.0	2	33.5	3311.0
77.0	77.4	4	44.7	3909.5
77.4	83.9	3	38.2	3630.5
83.9	89.5	4	44.7	3909.5
89.5	96.0	3	38.2	3630.5
96.0	106.7	4	44.7	3909.5
106.7	110.9	5	55.4	4071.2
110.9	121.5	4	44.7	3909.5
121.5	150.0	5	55.4	4071.2

⋮

Drug 4, Optimal Decisions for $s = 13$

Int Start	Int End	j^*	b_{4,j^*}	e_{4,j^*}
40.8	52.9	1	0	0
52.9	65.1	2	33.5	3311.0
65.1	65.8	3	38.2	3630.5
65.8	66.3	2	33.5	3311.0
66.3	67.1	3	38.2	3630.5
67.1	70.0	2	33.5	3311.0
77.0	77.4	3	38.2	3630.5
77.4	78.3	4	44.7	39095
78.3	81.4	3	38.2	3630.5
81.4	83.9	4	44.7	39095
83.9	84.8	3	38.2	3630.5
84.8	85.7	4	44.7	39095
85.7	86.0	3	38.2	3630.5
86.0	86.3	4	44.7	39095
86.3	86.6	3	38.2	3630.5
86.6	86.9	4	44.7	39095
86.9	87.8	3	38.2	3630.5
87.8	88.2	4	44.7	39095
88.2	88.6	3	38.2	3630.5
88.6	89.5	4	44.7	39095
89.5	90.4	3	38.2	3630.5
90.4	116.0	4	44.7	39095
116.0	150.0	5	55.4	4071.2

⋮

Drug 7, Optimal Decisions for all s

Int Start	Int End	j^*	b_{4,j^*}	e_{4,j^*}
0.0	12.1	1	0	0
12.1	13.9	2	12.1	5433.8
13.9	16.4	3	13.9	5981.5
16.4	20.4	4	16.4	6476.7
20.4	150.0	5	20.4	6807.5

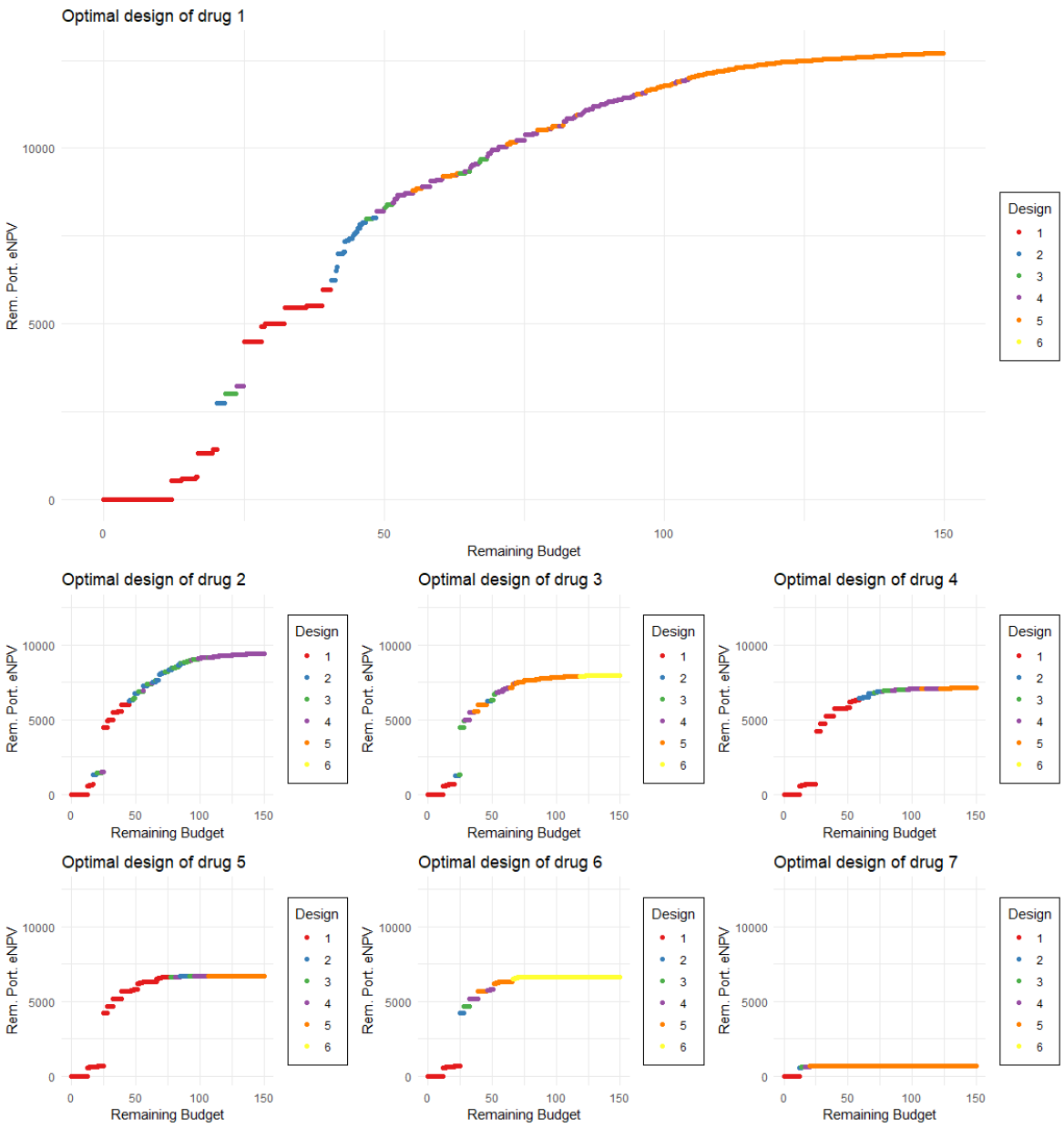

Figure 6-9: The optimal decisions for each drug in the case where no GSDs are ongoing (that is, $s = 1$) for Case Study 2. For each drug and portfolio remaining budget, each plot gives the optimal design for the drug (given by the colour) and the expected gain of the rest of the portfolio including the current drug.

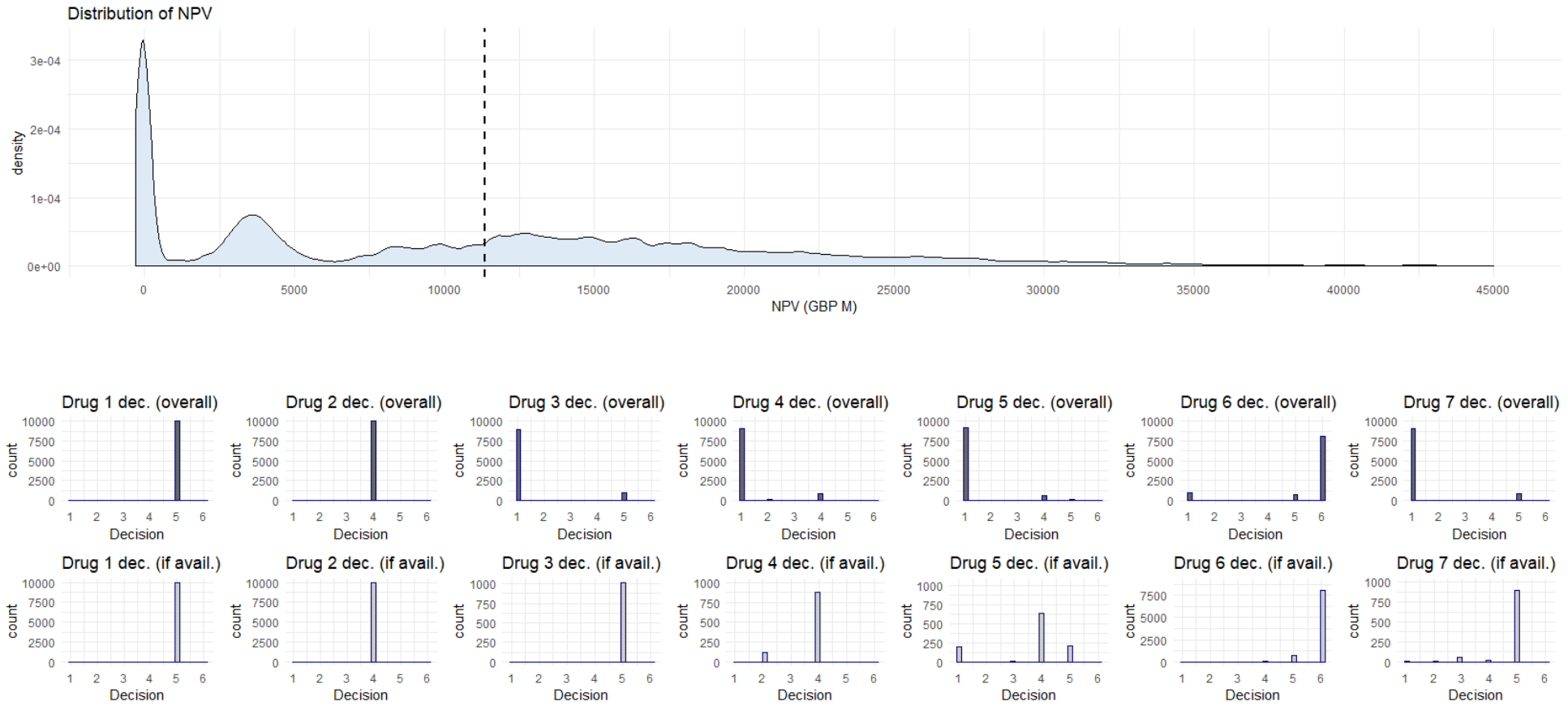

Figure 6-10: (Top) The distribution of the expected gain of the portfolio for Case Study 2, given as a density plot using the simulation method described in Section 6.6. (Bottom) The histograms show distribution of the designs chosen given one follows the optimal decisions.

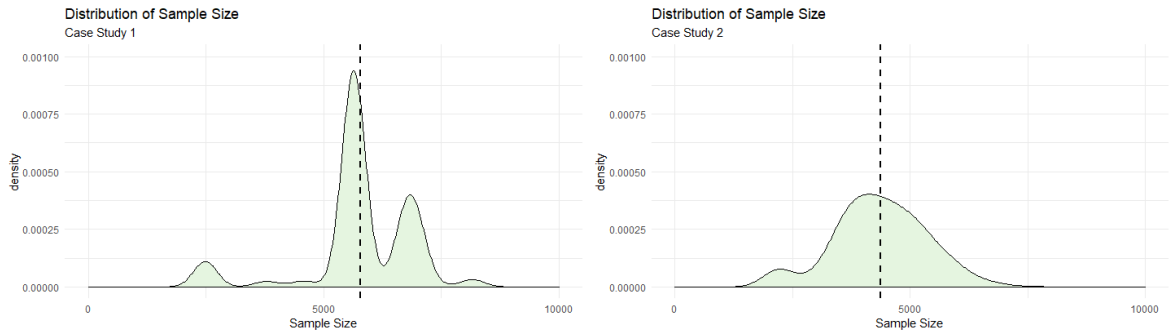

Figure 6-11: The distribution of sample size from simulations given one follows the optimal decision rules, for case studies 1 and 2.

The GSDs in this case study may also be of different types, for example, we might consider the 1 sided rho-family error spending GSDs defined by Jennison and Turnbull (2000). When the GSDs are of this type with $\rho = 2$, one obtains similar decision rules and expected gains.

The benefit of Group Sequential Designs

As noted at the beginning of this case study, the benefits of group sequential designs in a portfolio are two-fold. Firstly, stopping early for efficacy allows one to market the drug for longer until patent expiry, and secondly stopping early for efficacy or futility saves resources which can be returned back into the portfolio budget to invest in future drugs. The group sequential designs for Drugs 1 and 6 greatly increase the contributions to eNPV from both of these drugs, and other drugs near the end of the portfolio, and at the expense of other drugs near the start of the portfolio.

Keeping track of the group sequential situation ID to track when ongoing group sequential trials may terminate early and return budget to the portfolio is the main driver in increasing the computational complexity of the algorithm. One may ask if one was to ignore this mechanism and assume no budget gets returned when a group sequential trial stops early, what is the value of the portfolio? One may run the dynamic programming algorithm again to find new optimal decision rules and a corresponding portfolio expected gain by treating all designs as fixed sample (hence dramatically decreasing the computational workload) whilst using the eNPV and budgets of the group sequential designs for Drugs 1 and 6 from the original Case Study 2. We present the results of this in Table 6.12.

Table 6.12: The expected gain from the dynamic programming algorithm from (i) the original Case Study 2, (ii) Case Study 2 when one assumes leftover budget from group sequential trials stopping early is not reinvested back into the portfolio, and (iii) Case Study 1.

	Expected Gain
Case Study 2	*12 654*
Case Study 2 with no return of leftover budgets	*12 527*
Case Study 1	*11 834*

From this case study, it looks like the longer time until patent expiry is the main driver in increasing the portfolio expected gain. Furthermore, in Case Study 5, we consider the benefit of having group sequential designs with only futility boundaries.

6.7.3 Case Study 3: A fully group sequential portfolio

In this case study, we look at the impact of allowing all drugs to have a GSD. As more GSDs are used in the portfolio, the complexity of the problem increases as the number of possible GSD situation IDs s in the state space increased. To simplify the problem in other areas, we consider a portfolio with 1 trial per Phase III and fewer design choices. We shall specify two portfolios to compare against one another- one with no GSDs and the other with GSDs for all drugs. The inputs are specified below.

Inputs

Total portfolio budget of \$60M. In Table 6.13, we display the inputs for Case Study 3 when no drug have group sequential designs (*All Fixed Sample*).

Table 6.13: Inputs for Case Study 3: no drug have group sequential designs (*All Fixed Sample*)

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
a_i	1	1	3	6	13	18	25
$p_i^{(a)}$	1	1	0.1	0.1	0.1	0.9	0.1
p_i^{eff}	0.5	0.5	0.5	0.5	0.5	0.5	0.5
α_i	0.05	0.05	0.05	0.05	0.05	0.05	0.05
σ_i	2	1.8	2	2	1.5	1.5	1
λ_i	20	30	90	45	60	90	45
c_i	11.09	16.64	25.29	23.63	25.79	14.84	14.01
f_i	2805	15	525	2125	240	125	500
T_i^P	108	120	135	180	155	180	145
t_i^s	6.3	7	18	18	30	12	18
F_i	50000	500000	400000	300000	500000	300000	1000000
R_i^{mean}	175000	85000	400000	200000	45000	250000	500000
R_i^{sd}	35000	17000	80000	40000	9000	50000	100000
μ_1	0.5	0.4	0.5	0.4	0.4	0.3	0.25
μ_0	0	0	0	0	0	0	0
t_{trt}	0.3	1	12	12	24	6	12
n_i^{trials}	1	1	1	1	1	1	1
ρ	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083
GSD?	No	No	No	No	No	No	No
GSD Type							
GSD # Analyses							
$1-\beta_{i,1}$	0	0	0	0	0	0	0
$1-\beta_{i,2}$	0.80	0.80	0.80	0.80	0.80	0.80	0.80
$1-\beta_{i,3}$	0.90	0.90	0.90	0.90	0.90	0.90	0.90
$1-\beta_{i,4}$	0.95	0.95	0.95	0.95	0.95	0.95	0.95

In Table 6.14, we display the inputs for Case Study 3 when all drugs have group sequential designs (*All GSDs*).

Table 6.14: Inputs for Case Study 3: all drugs have group sequential designs (*All GSDs*)

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
a_i	1	1	3	6	13	18	25
$p_i^{(a)}$	1	1	0.1	0.1	0.1	0.9	0.1
p_i^{eff}	0.5	0.5	0.5	0.5	0.5	0.5	0.5
α_i	0.05	0.05	0.05	0.05	0.05	0.05	0.05
σ_i	2	1.8	2	2	1.5	1.5	1
λ_i	20	30	90	45	60	90	45
c_i	11.09	16.64	25.29	23.63	25.79	14.84	14.01
f_i	2805	15	525	2125	240	125	500
T_i^P	108	120	135	180	155	180	145
t_i^s	6.3	7	18	18	30	12	18
F_i	50000	500000	400000	300000	500000	300000	1000000
R_i^{mean}	175000	85000	400000	200000	45000	250000	500000
R_i^{sd}	35000	17000	80000	40000	9000	50000	100000
μ_1	0.5	0.4	0.5	0.4	0.4	0.3	0.25
μ_0	0	0	0	0	0	0	0
t_{trt}	0.3	1	12	12	24	6	12
n_i^{trials}	1	1	1	1	1	1	1
ρ	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083
GSD?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
GSD Type	TS	TS	TS	TS	TS	TS	TS
GSD # Analyses	3	3	3	3	3	3	3
$1-\beta_{i,1}$	0	0	0	0	0	0	0
$1-\beta_{i,2}$	0.80	0.80	0.80	0.80	0.80	0.80	0.80
$1-\beta_{i,3}$	0.90	0.90	0.90	0.90	0.90	0.90	0.90
$1-\beta_{i,4}$	0.95	0.95	0.95	0.95	0.95	0.95	0.95

Results

We see a significant increase in the portfolio value when drugs are allowed to have GSDs.

	All Fixed Sample	*All GSDs*
Portfolio eNPV	12 503	13 480
sd of Portfolio NPV	*9 448*	*10 124*

Below, in Figures 6-12, 6-13, 6-14, and 6-15 we plot the optimal decision rules and distribution of portfolio value in the *All Fixed Sample* and *All GSDs* case.

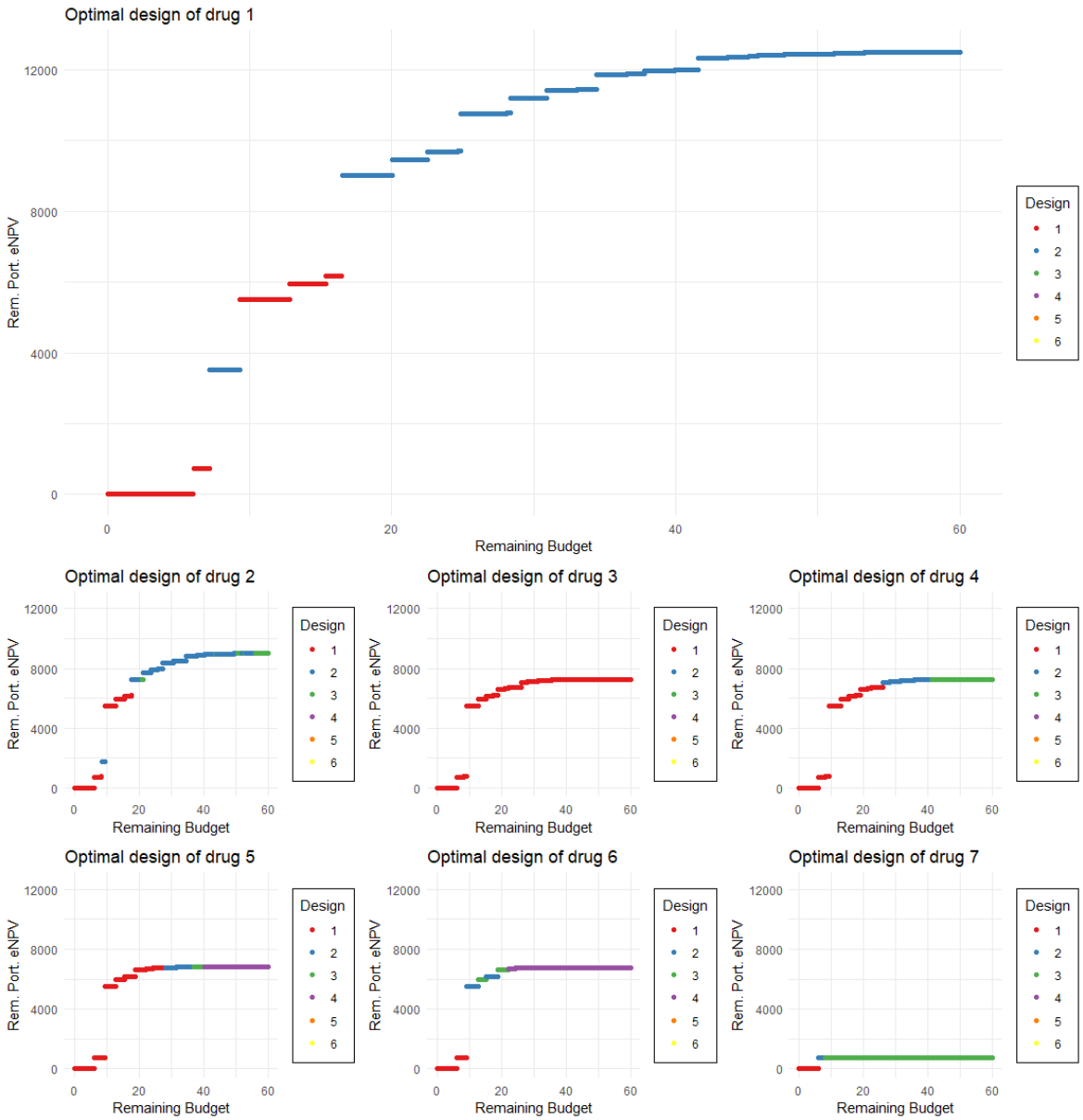

Figure 6-12: *All Fixed Sample*: The optimal decisions for each drug. For each drug and portfolio remaining budget, each plot gives the optimal design for the drug (given by the colour) and the expected gain of the rest of the portfolio including the current drug when no GSDs are ongoing (that is, $s = 1$).

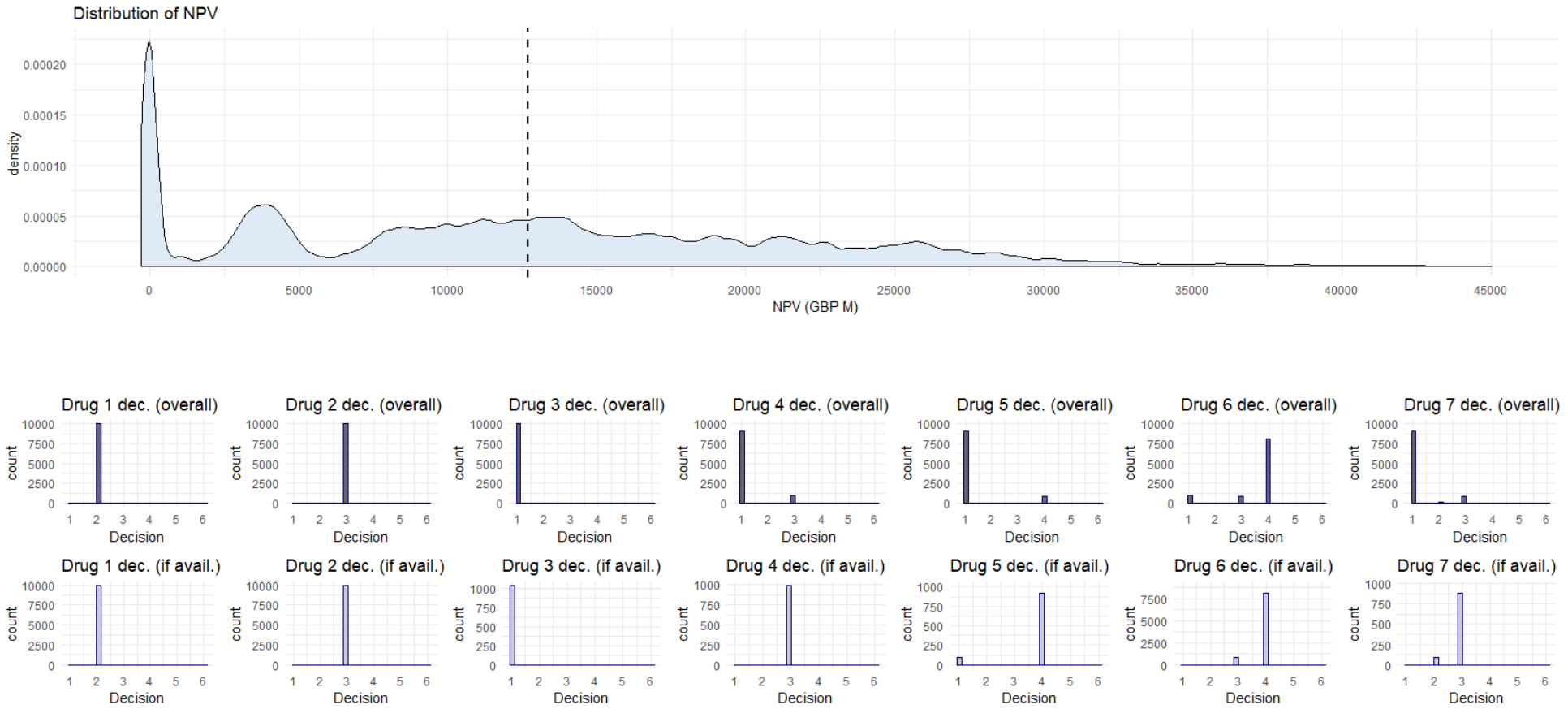

Figure 6-13: *All Fixed Sample*: (Top) The distribution of the expected gain of the portfolio, given as a density plot using the simulation method described in Section 6.6. (Bottom) The histograms show distribution of the designs chosen given that one follows the optimal decisions.

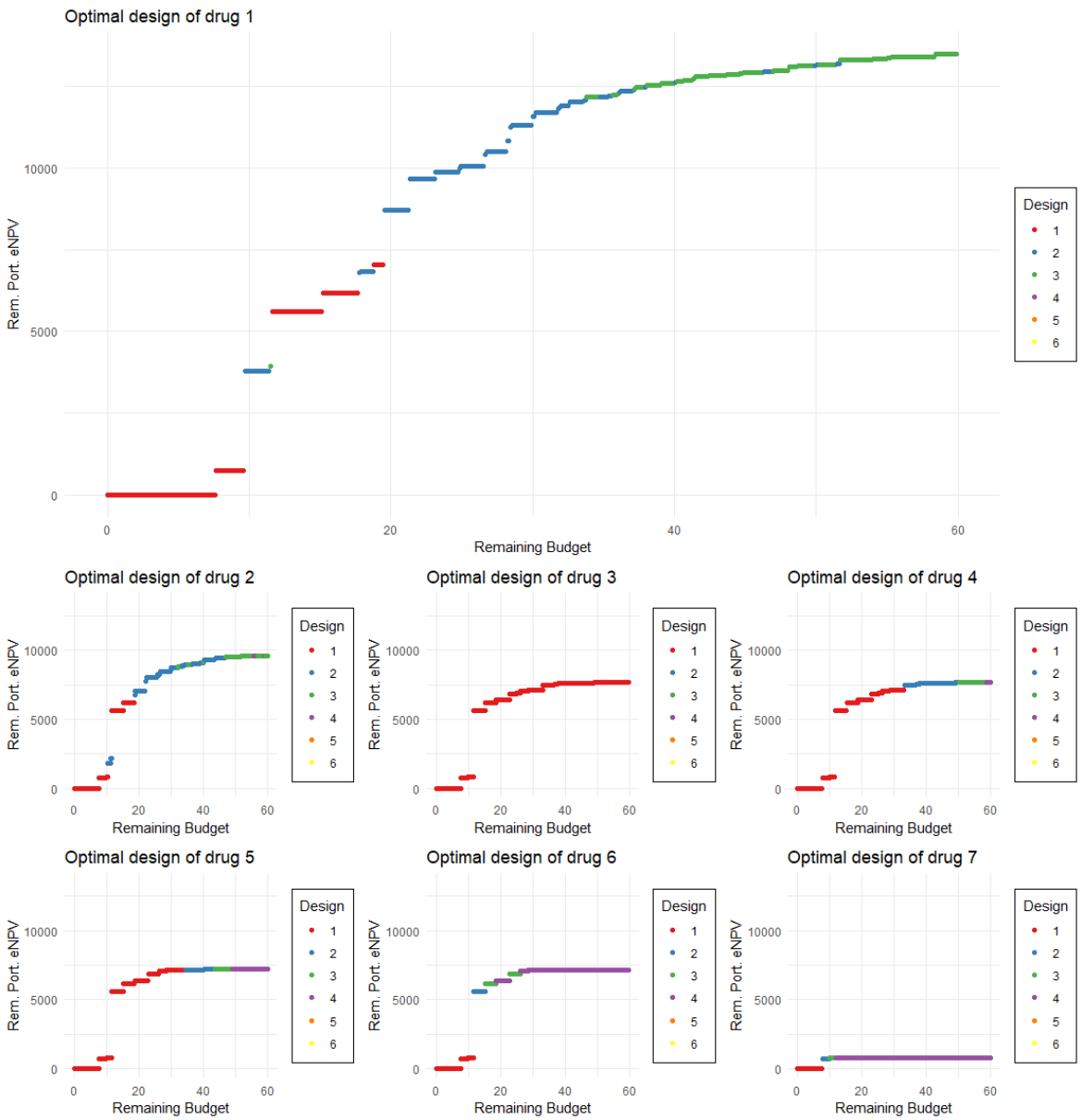

Figure 6-14: *All GSDs*: The optimal decisions for each drug. For each drug and portfolio remaining budget, each plot gives the optimal design for the drug (given by the colour) and the expected gain of the rest of the portfolio including the current drug when no GSDs are ongoing (that is, $s = 1$).

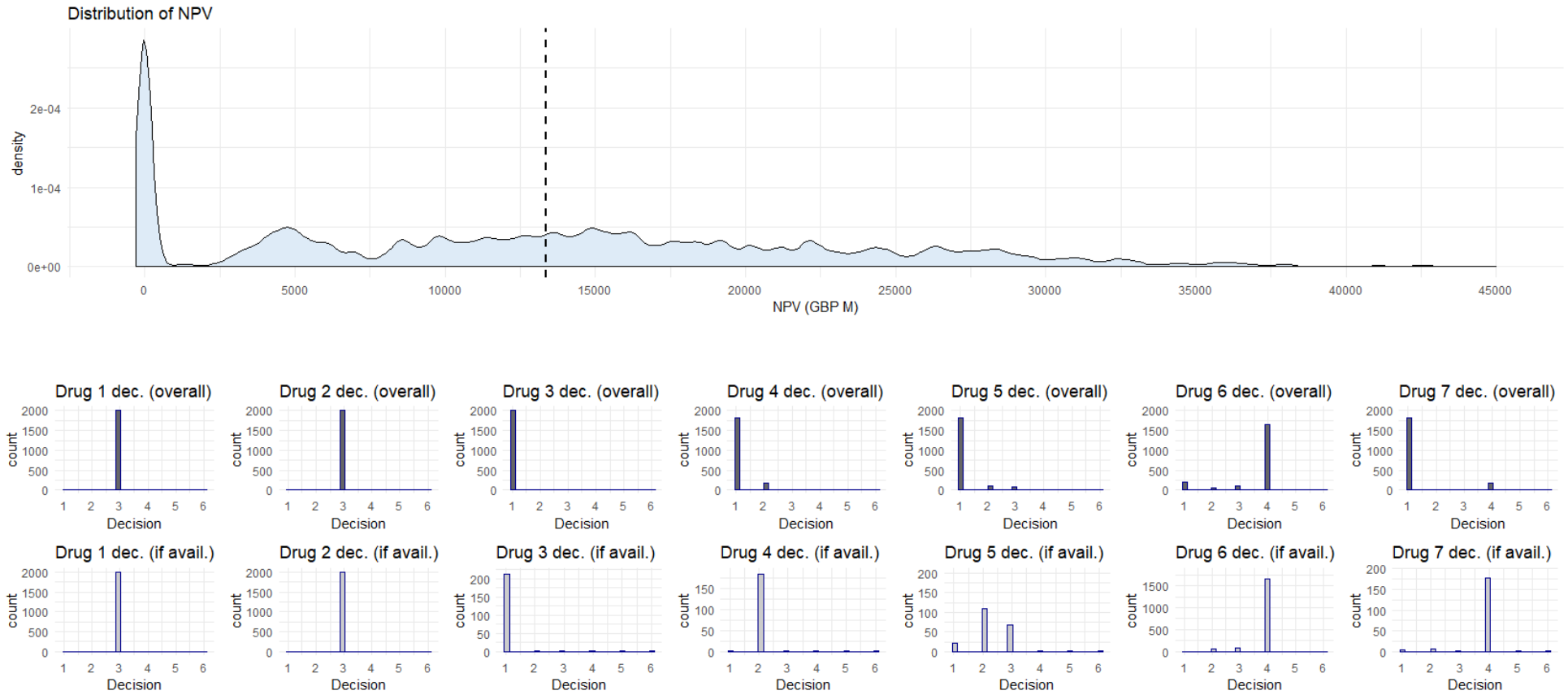

Figure 6-15: *All GSDs*: (Top) The distribution of the expected gain of the portfolio, given as a density plot using the simulation method described in Section 6.6. (Bottom) The histograms show distribution of the designs chosen given one follows the optimal decisions.

Computational workload

If the portfolio is restricted to fixed sample designs, the computational expense required is not an issue even for a large number of drugs (as shown in Case Study 1). As GSDs are added to the portfolio, the number of values s can take increases exponentially meaning the state space for each drug grows rapidly. This is especially the case when there are multiple Phase III GSD trials for each drug. In this case study with a single group sequential design for each of the 7 drugs, we reach the limit of computational feasibility for a reasonable time (1 day) with a dedicated CPU with 16 cores.

6.7.4 Case Study 4: Competitor drugs

In real life portfolio decision making problems, one would not consider one's own portfolio in isolation, but would make use of external information. The market for pharmaceutical products is competitive, and several pharmaceutical companies may be developing drugs for the same therapeutic area. It is possible to consider when rival products from other pharmaceutical companies will go to market, and to make decisions about one's own portfolio based on this knowledge.

Being *first to market* is to market one's own drug before a rival company markets a similar drug they are working on. This is an important consideration in portfolio decision making. Those drugs without possible competitors may justify a greater proportion of investment compared to those with possible competitor drugs.

To understand how the consideration of competitor drugs impacts decision making within the portfolio, one may specify this within the portfolio model. One may stipulate for each drug whether there is a potential competitor drug, the probability that this competitor drug will reach market p_i^{comp}, the time this competitor drug will go to market t_i^{comp}, and the market share that the competitor will take from the revenue $\mathfrak{r}_i^{\text{comp}}$. If the competitor drug for drug i is successful, and will take a market share of 50%, the revenue per month will be reduced by 50% at all times the competitor drug is also marketed.

We propose a case study similar to Case Study 1 which has only fixed sample designs, but with some drugs having competitor drugs. We examine how this affects the portfolio value and optimal decisions.

Inputs

We specify the same parameters as Case Study 1 with fixed sample designs only, with a total portfolio budget of \$150M, but also specify characteristics of any potential competitor drugs. These inputs are given in Table 6.15.

Table 6.15: Inputs for Case Study 4

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
$t_i^{(a)}$	1	1	3	6	13	18	25
$p_i^{(a)}$	1	1	0.1	0.1	0.1	0.9	0.1
p_i^{eff}	0.5	0.5	0.5	0.5	0.5	0.5	0.5
α_i	0.05	0.05	0.05	0.05	0.05	0.05	0.05
σ_i	2	1.8	2	2	1.5	1.5	1
λ_i	20	30	90	45	60	90	45
c_i	11.09	16.64	25.29	23.63	25.79	14.84	14.01
f_i	2805	15	525	2125	240	125	500
T_i^P	108	120	135	180	155	180	145
t_i^s	6.3	7	18	18	30	12	18
F_i	50000	500000	400000	300000	500000	300000	1000000
R_i^{mean}	175000	85000	400000	200000	45000	250000	500000
R_i^{sd}	35000	17000	80000	40000	9000	50000	100000
μ_1	0.5	0.4	0.5	0.4	0.4	0.3	0.25
μ_0	0	0	0	0	0	0	0
t_{trt}	0.3	1	12	12	24	6	12
n_i^{trials}	2	2	2	2	2	2	2
ρ	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083
Competitor?	Yes	Yes	No	Yes	Yes	Yes	No
t_i^{comp}	33	5		66	30	30	
p_i^{comp}	0.75	0.10		0.95	0.5	0.5	
$\mathfrak{r}_i^{\text{comp}}$	0.60	0.25		0.95	0.25	0.5	
$1-\beta_{i,1}$	0	0	0	0	0	0	0
$1-\beta_{i,2}$	0.80	0.80	0.80	0.80	0.80	0.80	0.80
$1-\beta_{i,3}$	0.85	0.85	0.85	0.85	0.85	0.85	0.85
$1-\beta_{i,4}$	0.90	0.90	0.90	0.90	0.90	0.90	0.90
$1-\beta_{i,5}$	0.95	0.95	0.95	0.95	0.95	0.95	0.95
$1-\beta_{i,6}$	0.99	0.99	0.99	0.99	0.99	0.99	0.99

Results

	Case Study 1	Case Study 4
Portfolio eNPV	11 834	8 775
sd of Portfolio NPV	*9 325*	*7 753*

The competitor drugs reduce the portfolio value by a quarter, due to the lost revenues due to competitor drugs taking away a share of the market. In Case Study 1 one saw that most revenue is generated from Drugs 1 and 6. In Case Study 4 there is a high probability of the competitor drug being available from most of the remaining patent life time of these drugs. There is also additional uncertainty (as a ratio of standard deviation to mean of portfolio NPV) around the value of the portfolio due to whether or not the competitor drug goes to market.

In Figures 6-16 and 6-17, we show the optimal decisions for each drug and the distribution of gain when one follows these optimal decisions.

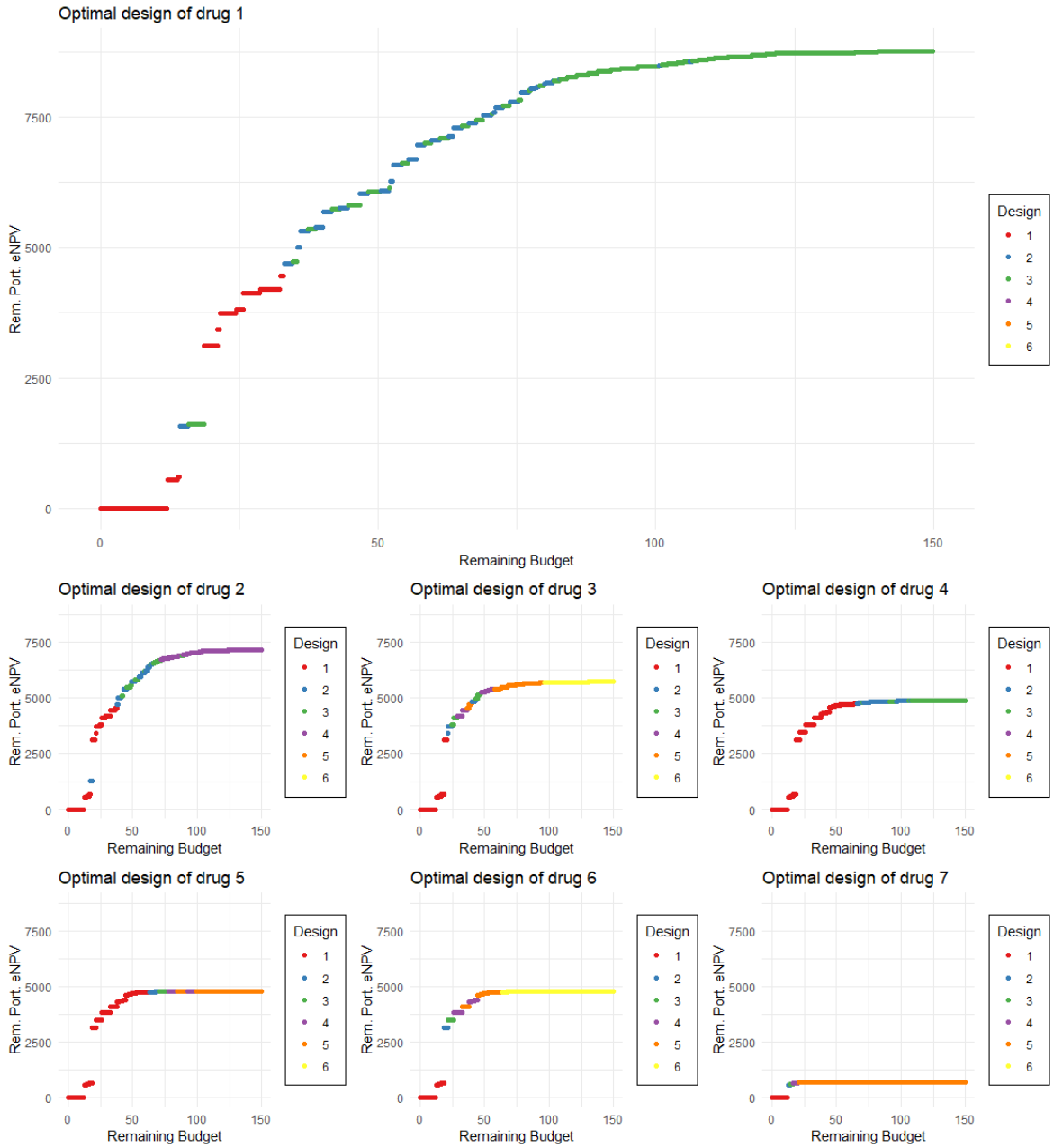

Figure 6-16: The optimal decisions for each drug. For each drug and portfolio remaining budget, each plot gives the optimal design for the drug (given by the colour) and the expected gain of the rest of the portfolio including the current drug.

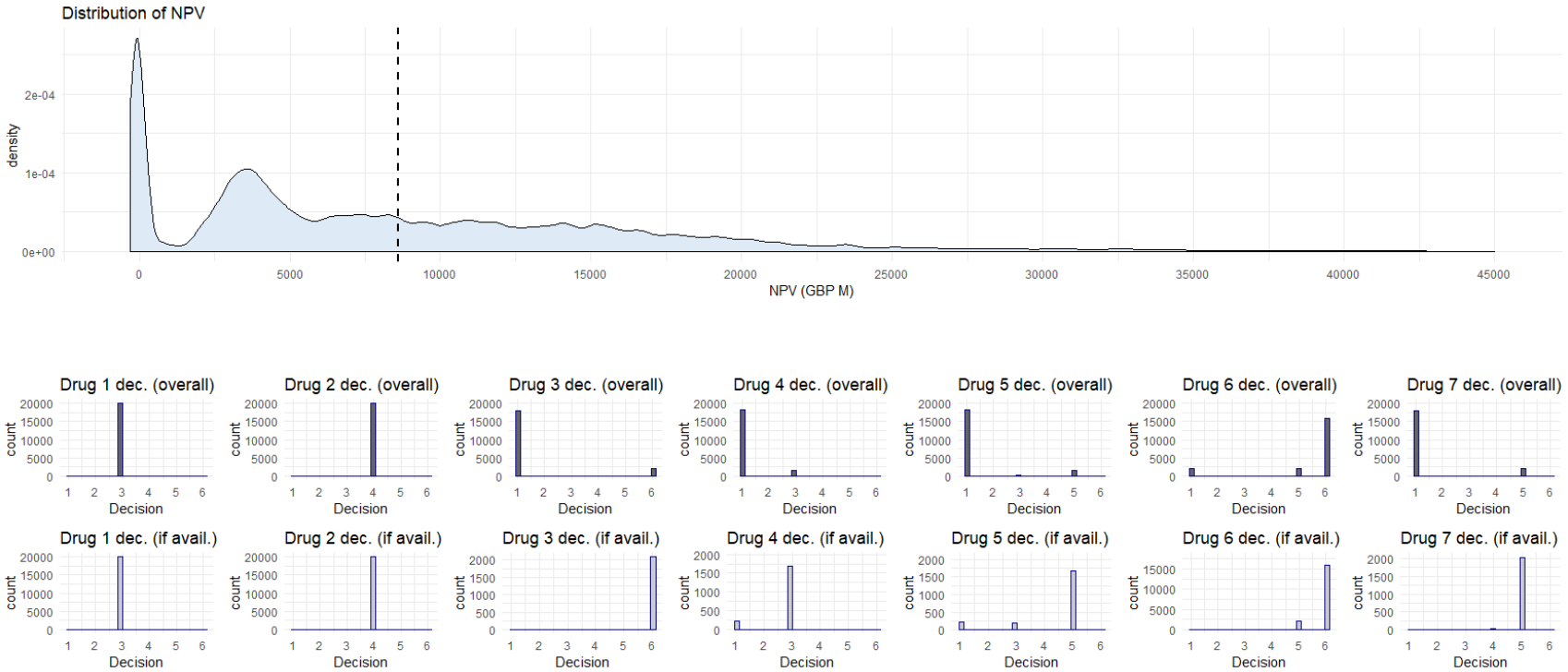

Figure 6-17: (Top) The distribution of the expected gain of the portfolio, given as a density plot using the simulation method described in Section 6.6. (Bottom) The histograms show distribution of the designs chosen given one follows the optimal decisions.

The impact of competitor drugs within the portfolio

Comparing the optimal decisions in Figures 6-5 and 6-17, we note that for when a competitor is present, the optimal decisions are to invest comparably less budget into these drugs. For example, Drugs 1 and 4 are likely to have a competitor which takes away a large proportion of the revenue. The optimal decisions for these drugs in Figure 6-17 are both Design 3 if available compared to Design 4 and 5 respectively in Figure 6-6 in Case Study 1 where competitor drugs are not present. The presence of competitors for each drug decreases the expected gain for that drug, meaning one cannot justify as large a budget investment as before in most cases. Furthermore, it is more advantageous to use smaller trials that finish sooner that one can market the drug for longer before the competitor arrives and reduces the revenue.

Realistically, the presence of competitor drugs that possibly arrive at a certain time would perhaps influence sponsors to perform the trial more quickly to reach market sooner. In our portfolio model, this may only be done by reducing the sample size. Practically, there may be many methods to achieve this, such as using more centres in parallel to reach the required sample size in a shorter time frame. Depending on the circumstances, this may be a better solution than the one suggested by the optimal decision rules in this model.

This case study shows how considerations about competitor drugs can be easily incorporated into the portfolio problem with minimal extra computations.

6.7.5 Case Study 5: A minimum number of patients for safety?

The purpose of Phase III in drug development is not solely the examination of efficacy of the treatment. The safety of the drugs must be monitored, and one may require a certain number of patients to be on the treatment group in order to satisfy company and regulatory guidelines. In this case, very early stopping for efficacy will not be possible. In this case study, we examine the extent to which the gain to the portfolio when the scope for using group sequential designs as shown in Case Study 2 is curtailed by requiring a safety stipulation of no early stopping for efficacy, or a minimum number of patients for each drug before stopping for efficacy is permitted.

As noted in Case Study 2, the benefit of using group sequential methods in a portfolio is two-fold. Firstly, stopping early for efficacy allows the drug to be marketed for longer until the patent expires, and secondly, stopping early for futility allows the remaining budget to be reinvested back into the portfolio. Using GSDs with only a futility boundary (referred to as *futility only GSD*s) will let us examine which of these factors contributes more to the increase in gain.

To investigate this, we propose (A) GSDs with only futility boundaries. We use the one-sided rho-family error spending designs as in Jennison and Turnbull (2000), where all boundaries except at the final analysis for stopping for efficacy are constrained to be infinity. Secondly, we propose (B) GSDs which specify a minimum number of patients for each Phase III trial to be on the treatment group and which stop for efficacy only if this requirement has been satisfied. In Figure 6-18, we show how one may construct the type of GSD as in case (B).

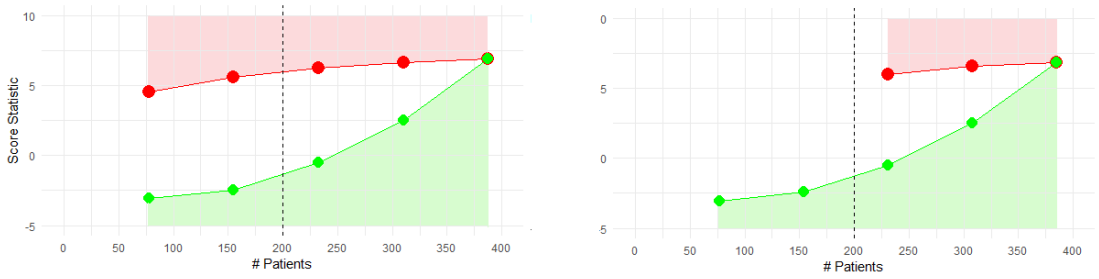

Figure 6-18: In the case (B), we require a minimum number of patients of 200 per arm. The error spending GSD (left) can be recomputed (right) to allow for this requirement. Note that all boundaries shift slightly to counter the absence of stopping for efficacy at the first two analyses.

Inputs

We use the same parameters as Case Study 2, with a total portfolio budget of $150M. We split the case study up into studying a portfolio with futility only GSDs (5A) and one with GSDs with a minimum number of patients required before stopping for efficacy (5B). We list the common parameters in Table 6.16 with the inputs for the GSDs in Tables 6.17 and 6.18.

Table 6.16: Parameters for Case Study 5

	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Drug 6	Drug 7
a_i	1	1	3	6	13	18	25
$p_i^{(a)}$	1	1	0.1	0.1	0.1	0.9	0.1
p_i^{eff}	0.5	0.5	0.5	0.5	0.5	0.5	0.5
α_i	0.05	0.05	0.05	0.05	0.05	0.05	0.05
σ_i	2	1.8	2	2	1.5	1.5	1
λ_i	20	30	90	45	60	90	45
c_i	11.09	16.64	25.29	23.63	25.79	14.84	14.01
f_i	2805	15	525	2125	240	125	500
T_i^P	108	120	135	180	155	180	145
t_i^s	6.3	7	18	18	30	12	18
F_i	50000	500000	400000	300000	500000	300000	1000000
R_i^{mean}	175000	85000	400000	200000	45000	250000	500000
R_i^{sd}	35000	17000	80000	40000	9000	50000	100000
μ_1	0.5	0.4	0.5	0.4	0.4	0.3	0.25
μ_0	0	0	0	0	0	0	0
t_{trt}	0.3	1	12	12	24	6	12
n_i^{trials}	2	2	2	2	2	2	2
ρ	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083	0.0083
$1-\beta_{i,1}$	0	0	0	0	0	0	0
$1-\beta_{i,2}$	0.80	0.80	0.80	0.80	0.80	0.80	0.80
$1-\beta_{i,3}$	0.85	0.85	0.85	0.85	0.85	0.85	0.85
$1-\beta_{i,4}$	0.90	0.90	0.90	0.90	0.90	0.90	0.90
$1-\beta_{i,5}$	0.95	0.95	0.95	0.95	0.95	0.95	0.95
$1-\beta_{i,6}$	0.99	0.99	0.99	0.99	0.99	0.99	0.99

Table 6.17: Case Study 5A: Futility only GSD Boundaries

	Drug						
	1	2	3	4	5	6	7
GSD?	Yes	No	No	No	No	Yes	No
GSD Type	ES-Fut $\rho = 2$					ES-Fut $\rho = 2$	
GSD # Analyses	5					5	

Table 6.18: Case Study 5B: GSDs with minimum number of patients before stopping for efficacy

	Drug						
	1	2	3	4	5	6	7
Min # Patients	250	0	0	0	0	350	0
GSD?	Yes	No	No	No	No	Yes	No
GSD Type	ES $\rho = 2$					ES $\rho = 2$	
GSD # Analyses	5					5	

Results

In Table 6.19, we compare the expected gain of the portfolio of Case Studies 5A and 5B to the unconstrained case in Case Study 2 and when the designs are all fixed sample in Case Study 1. In Figures 6-19, 6-20, 6-21, and 6-22, we display the optimal decision rules for Case Studies 5A and 5B with the distribution of portfolio value when these optimal decision rules are followed.

Table 6.19: Expected gain of the portfolio in Case Study 1, 2, 5A, and 5B

	Case Study 1	Case Study 2	Case Study 5A	Case Study 5B
	Fixed Sample	*No Constraints*	*Futility Only*	*Min SS*
Portfolio Expected Gain	11 834	12 654	11 696	12 274
SD of Portfolio Gain	*9 325*	*9 782*	*9 834*	*9 466*

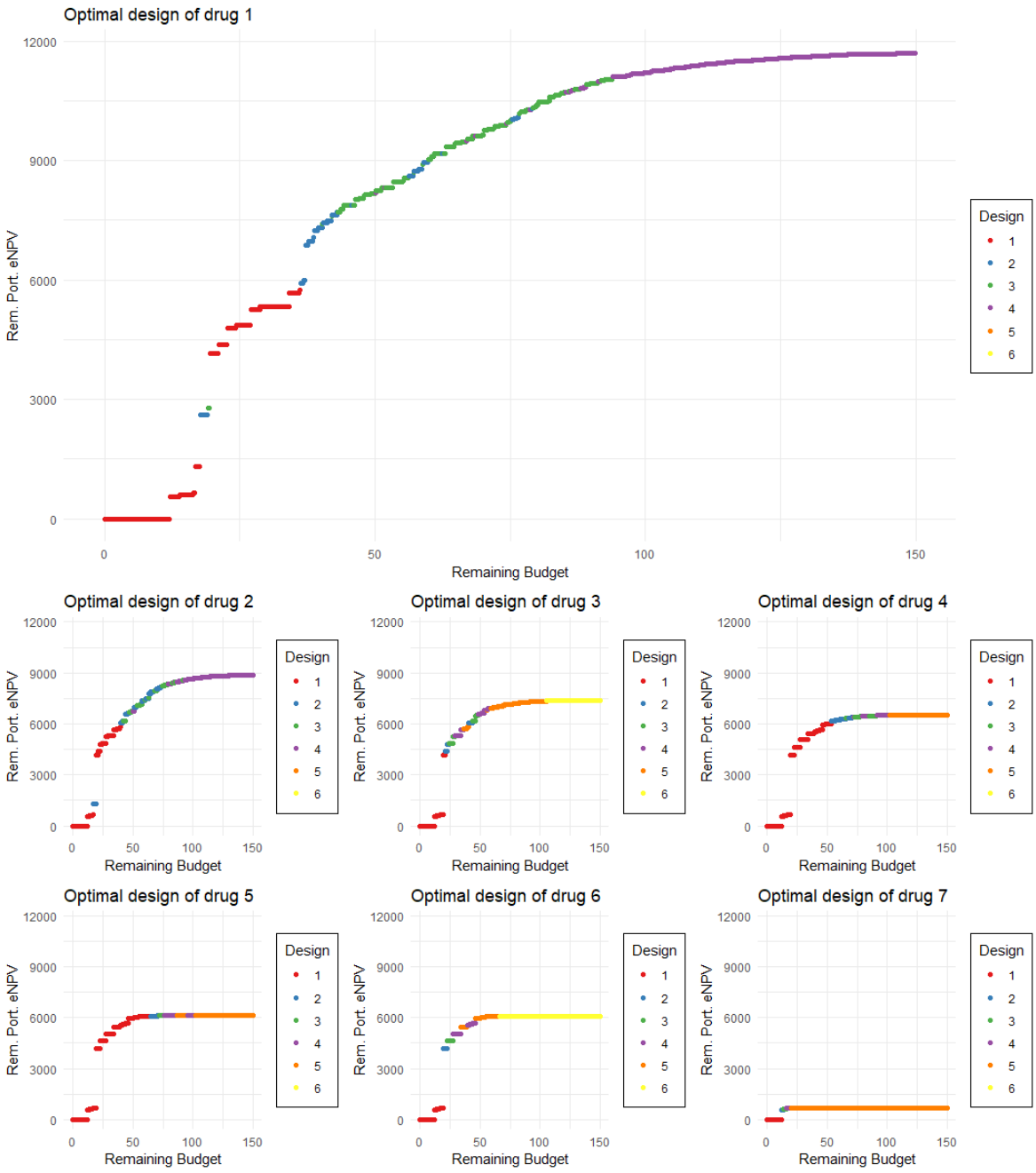

Figure 6-19: The optimal decisions for each drug for Case Study 5A. For each drug and portfolio remaining budget, each plot gives the optimal design for the drug (given by the colour) and the expected gain of the rest of the portfolio including the current drug.

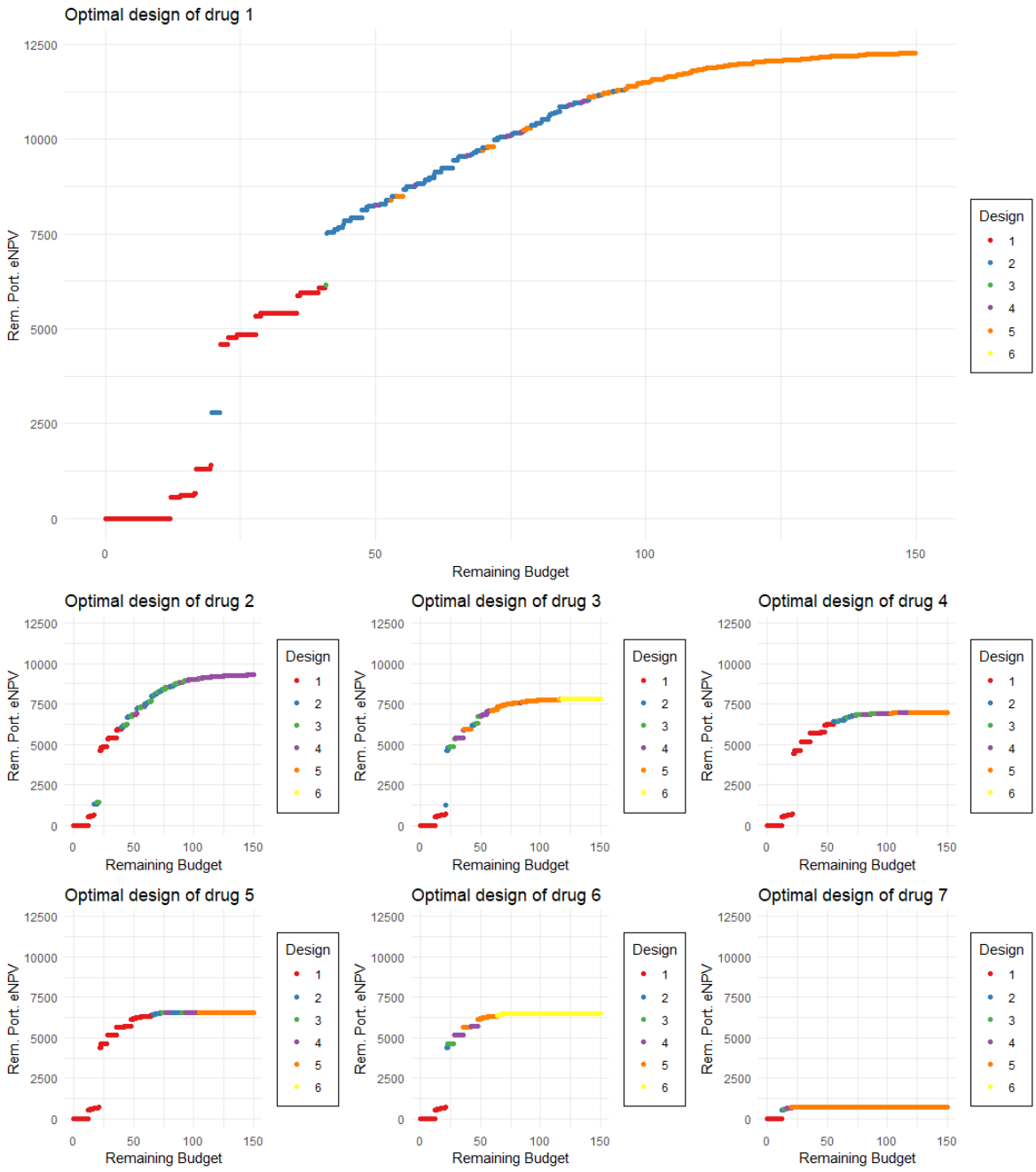

Figure 6-20: The optimal decisions for each drug for Case Study 5B. For each drug and portfolio remaining budget, each plot gives the optimal design for the drug (given by the colour) and the expected gain of the rest of the portfolio including the current drug.

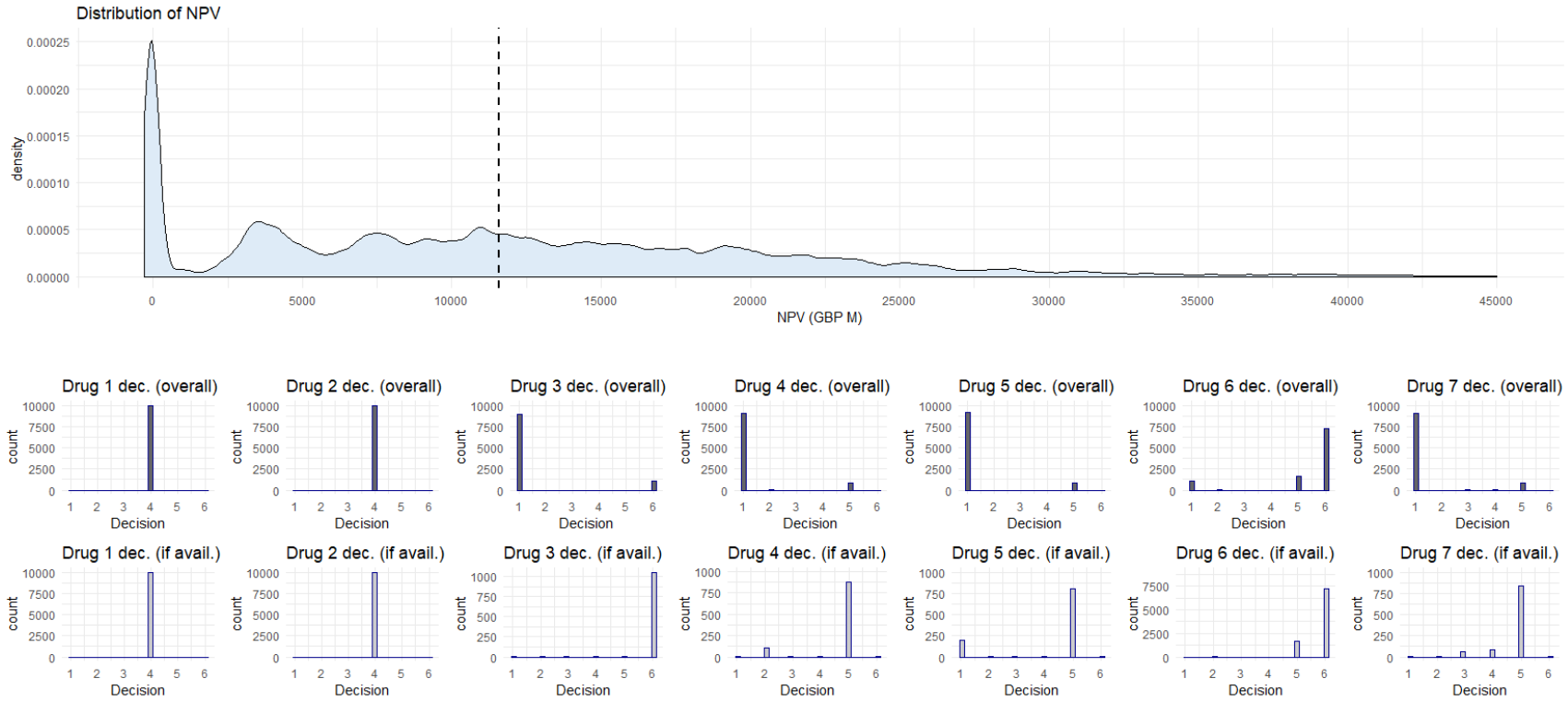

Figure 6-21: The distribution of the expected gain of the portfolio for Case Study 5A, given as a density plot using the simulation method described in Section 6.6. (Bottom) The histograms show distribution of the designs chosen given one follows the optimal decisions.

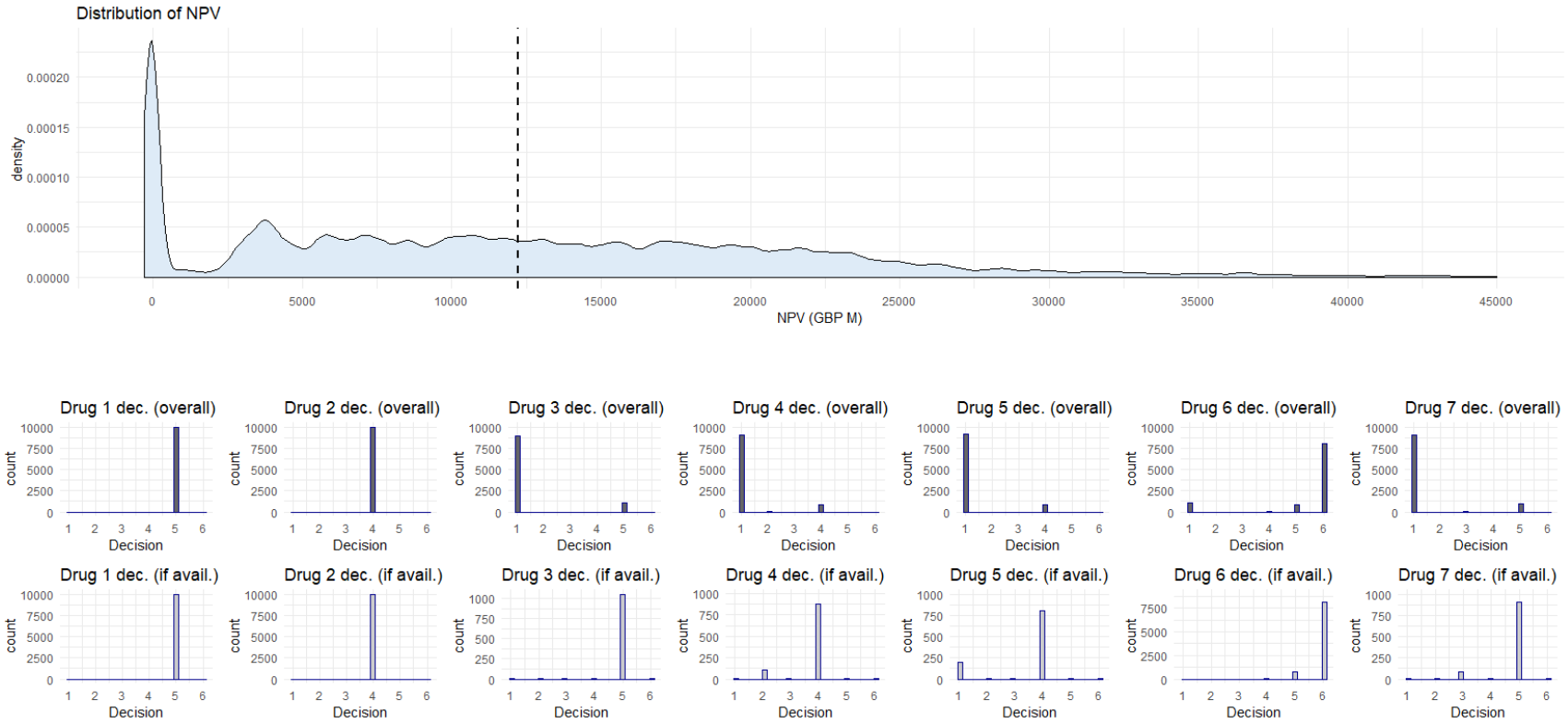

Figure 6-22: The distribution of the expected gain of the portfolio for Case Study 5B, given as a density plot using the simulation method described in Section 6.6. (Bottom) The histograms show distribution of the designs chosen given one follows the optimal decisions.

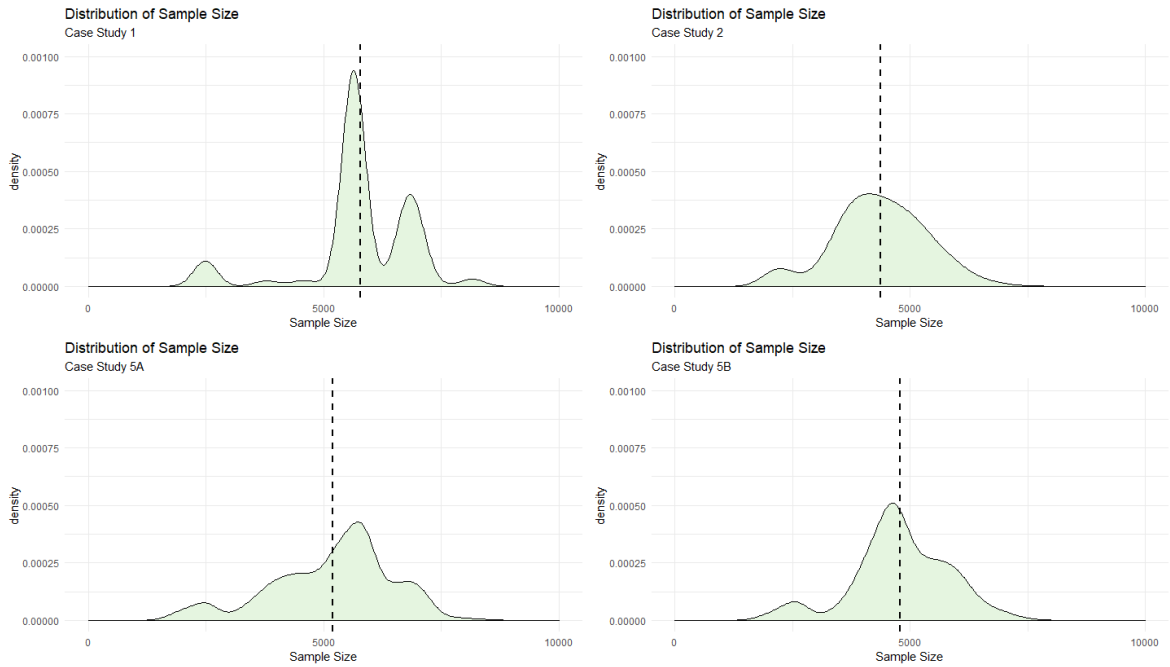

Figure 6-23: The distribution of sample size used in the simulations for Case Study 1,2, 5A, and 5B.

Portfolio Value

Comparing the value of the portfolio for fixed sample designs (Case Study 1), and futility-only GSDs (Case Study 5A) in Table 6.19, we see that the scheme with fixed sample designs has a higher eNPV. The longer trials required for the GSDs harms the value of the portfolio more than the benefit obtained from stopping early for futility with reinvestment of the remaining budget back into the portfolio. The benefit of futility-only GSDs comes from reinvesting leftover budget back into the portfolio. There is no advantage of this from Drug 6 which is at the end of the portfolio. Any advantage from Drug 1 is mitigated by the longer maximum sample size required for Drugs 1 and 6 compared to fixed sample designs in order to have early stopping boundaries. These longer maximum sample sizes reduce the time until patent expiry and this reduces the revenue. Thus, at least in this portfolio, it appears that the gain from using group sequential methods (in Case Study 2) comes primarily from the positive trials which have longer for marketing before patent expiry. This may not be the case in other portfolios with a smaller total budget, meaning there is a greater opportunity cost of not stopping early for futility to save funds for future drugs.

The above findings mirror similar findings in Antonijevic (2016) where it was found that a portfolio with adaptive elements (in particular stopping early for futility or sample size re-estimation) reduces the value of the portfolio relative to a portfolio with only fixed sample designs.

The minimum number of patients for drugs 1 and 6 in Case Study 5B means that one may stop early for efficacy at some interim analyses prior to the final analysis. Constructing the GSDs like this increases the value of the portfolio to 12 274 compared to Case Study 1, approximately half of the gain to the portfolio of using GSDs with no minimum number of patients as in Case Study 2.

We conclude that for this portfolio, the benefit of GSDs comes overwhelmingly from stopping early for efficacy. However, if a minimum number of patients is required for safety data, there is still added value in having GSDs which stop for efficacy once this minimum requirement

has been satisfied. For other portfolios in which the portfolio budget is lower, saving budget through futility only GSDs may be desirable.

Portfolio Sample Size

Even though the portfolio value accounts for the financial value of treating patients, using fewer patients may be desirable to make the process more ethical. Figure 6-23 shows the distribution of the sample size for programmes 1, 2, 5A, and 5B.

From this figure, the expected sample size is clearly significantly smaller for any portfolios that have group sequential methods (2, 5A, 5B). In addition, portfolios 5A and 5B only have a slightly higher expected sample size than portfolio 2.

Thus, we recommend that this information is taken into account in decision making if the financial model does not explicitly deal with the ethical advantages of using fewer patients.

6.8 Discussion

Inferences from the Case Studies

The problem of developing a portfolio of drugs is a high-value complex problem with decisions involving many trade-offs. In this chapter we explored a range of case studies to identify the inferences one can make from the statistical formulation of the portfolio problem. It is hoped these inferences will provide insight about optimal strategies for this problem, which may be used to make better decisions. We conclude by summarising each of the case studies in this chapter to assess the insights obtained.

Case Study 1 was formulated to represent a realistic portfolio of drugs belonging to a large sponsor, perhaps within a single therapeutic area. The parameters were those specified in Patel et al. (2013) and the designs were fixed sample designs only. Some of these treatments are far more likely to reach Phase III than others, and some have much higher revenues than others.

The optimal decision rules computed by the dynamic programming method clearly show that the optimal decisions depend upon the current state; in this case being the total portfolio budget remaining. The optimal design for Drug 1 can change in response to a small change in the total portfolio budget due to the discrete nature of the decisions and the number of possible combinations of paths for the remainder of the drugs. When this occurs, there is usually not much difference between the expected gains for the different designs.

From the solution of the portfolio problem, one can obtain many useful inferences. These include the optimal decision rules for each drug and the distribution of the portfolio value given one follows these optimal decision rules. We considered the loss of value of the portfolio when optimal decisions were not made, and we found that the policy maximising the expected gain return ratio of each drug decision rule, subject to the return ratio exceeding a certain (optimised) threshold, (*Constrained EG current drug*) did not result in too great a loss of efficiency compared to the optimal decision rule.

In Case Study 2, we wanted to assess the benefit of having group sequential designs within the portfolio. It was found that allowing two drugs (which both had high probabilities of availability) to have group sequential designs increased the portfolio value by about 7%. This gain came from mainly stopping early for efficacy which allowed a longer marketing time

from patent expiry, rather than from allowing unused budget to be reinvested back into the portfolio when stopping early for either efficacy or futility.

Case Study 3 examined the computational challenge of allowing all 7 drugs to have group sequential designs. Simplifications to allow optimisation in this case were to have only one Phase III trial for each drug, and to reduce the number of designs from 6 to 4. Allowing the group sequential designs for this portfolio increased the eNPV from \$12,503M to \$13,480M (+7.8%).

Case Study 4 examined the effect that external influences would have on the portfolio. In particular, if competitors were developing drugs that would compete with drugs in the portfolio, how does this change the optimal decision rules and portfolio value? Intuitively, the portfolio problem showed us that in this case the optimal decisions are to use smaller sample sizes in Phase III for drugs with competitors due to a lower return ratio and a desire to finish sooner so as to market the drug for longer before the competitor was released.

Case Study 5 assessed how the benefit to a portfolio of having group sequential designs was mitigated if one required a minimum sample size in Phase III for safety reasons. It was found in this case study that if the safety requirement stipulated a sample size significantly less than the maximum sample size of the group sequential design and there is an interim analysis shortly after this point, then most of the benefit of group sequential designs were preserved. The lesson from the case study is that group sequential designs still add benefit, as long as the interim analyses are performed once the minimum number of patients for the safety threshold has been reached (and as long as this minimum number of patients is significantly less than the maximum number of patients under the group sequential design).

Strengths of the Approach

Portfolio Problem Formulation

The formulation of the portfolio problem is a statistical model which maximises the value of the portfolio by finding the optimal decision rules regarding Phase III sample sizes for each drug under a portfolio budget constraint. As described in Patel et al. (2013), this approach provides a more realistic solution to the portfolio problem than other models with no budget limits or no choice of design. In previous chapters of this thesis, the probability of success of each Phase III and other factors that impact the revenue would dominate the investment required. However, an overall portfolio budget limit means there is an opportunity cost of spending for one drug at the expense of missing out on another.

The model accounts for many sources of uncertainty within the portfolio. These include whether a drug will pass the phases prior to Phase III, whether Phase III will be successful, whether the drug is efficacious of not, and what the revenue per month will be. The stochastic element of the Phase III availability incorporates this uncertainty. Using Monte Carlo simulations of the portfolio will incorporate the other sources of uncertainty of the model.

Furthermore, sensitivity analysis can be done by running the model a series of times using modifications of parameters in the model.

The optimal decision rules can be re-derived as more information becomes available. For example, after a certain number of months, one may rerun the model to obtain updated optimal decision rules given the information that has been observed so far and taking into

account new drugs that may become available on the horizon as well as any extra portfolio budget allowances. In the paper of Patel et al. (2013), this is referred to as the model being able to perform dynamic re-optimisation as new information becomes available.

The Dynamic Programming Method

The dynamic programming method provides a far more efficient method to solve the portfolio problem than the stochastic integer programming method as in most previous literature; in particular, Patel et al. (2013). In Case Study 1, we show how the computational time required to compute the decision rules increases at a linear rate as the number of drugs increases when designs are fixed sample. In particular, for 25 drugs with the dynamic programming method, the time required was only 90 seconds. In Table 6.1 we compared the running times of the dynamic programming method with a budget remaining state space with the SIP method and the dynamic programming method with design history state space. It was found the SIP method and the design history state space method suffered as the number of drugs increased due to the exponentially increasing number of possible design histories. In particular, the SIP method would not compute in a sufficiently small time when the number of drugs in the portfolio was 9 or more.

Whilst integer programming and stochastic integer programming are popular techniques in operational research, dynamic programming has been used commonly in computing optimal designs in clinical trials as described in Chapter 1. For instance, the computation of group sequential design boundaries (Chapter 19.6.1 Jennison and Turnbull (2000), Barber and Jennison (2002), Jennison and Turnbull (2006), Hampson and Jennison (2013)). Using a solution based on dynamic programming is therefore appealing as researchers in adaptive designs may be more familiar with the concepts underlying the dynamic programming approach.

Limitations of the Portfolio Problem

Knowing financial model parameters a-priori

The portfolio problem requires that the financial model parameters are known at the time of computing the optimal decision rules. These include the probability of availability, recruitment rate, and the mean and standard deviation of the revenues. If these differ much from the assumed values, the computed optimal decision rules may no longer be optimal. However, many of these parameters will not be known in advance and *guesstimates* will need to be made, perhaps based on historical data. Once more information becomes available, the optimal decision rules can be dynamically updated by re-running the model with the new data.

Relationships between the efficacy of the drugs

The model assumes there is no relationship between the efficacy of different drugs. In particular settings such as basket, umbrella, or platform trials knowledge that one treatment is efficacious may lend weight to the belief that other treatments will be efficacious. Dependence between the efficacy of drugs is not easily incorporated within the dynamic programming

method, as this requires an extension of the state space to specify which drugs are found to be efficacious.

Portfolio familywise error rate

A portfolio familywise error rate may be defined as the probability of deducing at least one drug in the portfolio is efficacious when none are efficacious. Presently, each Phase III trial has a type I error which is pre-defined. When considering the portfolio problem as a whole, one could control the portfolio familywise error rate, allocating equal proportions of type I error to each drug such that the probability of making a type I error across all drugs is bounded by a pre-specified amount. However, this is not a necessary requirement of regulators and may be considered unnecessary.

Penalising the variability of the gain

A downside of the model is that it is based on optimising the eNPV of the portfolio. Although this is a commonly used criterion in decision making in many industries, it involves an indifference to risk. One may define an adjusted eNPV which negatively weights strategies involving more risk than others. The optimal decisions derived from this measure may be more suitable for smaller companies, or for those that require investment from venture capital firms.

Computations as the number of GSDs increase

A large part of the motivation for developing the dynamic programming method for the portfolio problem was the desire to study more complex portfolios involving group sequential designs. This was done by adding in an extra dimension to the state space, which takes the form of an integer ID tracks the current situation of all group sequential designs in the portfolio.

The size of the state space for each drug is the number of discretisations of the budget remaining dimension of the state space multiplied by the number of values this ID can take. The size of the state space grows exponentially as the number of drugs with group sequential designs increase, particularly if each drug has two Phase III trials. Therefore the method runs into computational difficulty once the number of drugs with group sequential designs increases beyond two or three. With simplifying assumptions, (such as in Case Study 3) one may be able to increase the number beyond this point.

Learning from Phase II efficacy information

In this framework we have assumed that drugs will either pass Phase II and be available for Phase III or not. Information about the performance of the drug in Phase II is not used for decision making purposes, in comparison to other approaches taken in this thesis, such as in Phase II/III programmes in Chapters 2 and 3.

Whilst making decisions about the Phase III trial based upon the posterior distribution of the treatment effect given Phase II data would be desirable, this would make the computations

more difficult, as optimal decisions must be stored for all values a variable describing the Phase II performance.

An alternative may be to have discrete states describing the drugs performance in Phase II, with different decision rules for each state. For example, a particular drug would either (i) not be available for Phase III, (ii) be available for Phase III with satisfactory performance in Phase II, or (iii) be available for Phase III with high performance in Phase II. The central equations in dynamic programming would require an extra term, but the dynamic programming algorithm would only require the computation of an optimal decision for (iii) in addition to (ii).

Going back for previous drugs

Suppose one does not invest in a particular drug in the hope of using the resources for future drugs, only for the future drugs not to be available. One may be tempted to go back to invest in the initial drug despite it becoming less attractive due to having a shorter patent life. In the framework considered, this is not allowed.

Looking Forward

Alternative mechanisms for the R&D portfolio budget

Conversations with stakeholders have brought interesting comments about how decision making works at a portfolio level within a therapeutic area at a large sponsor. It is suggested that R&D funding is not solely fixed at a portfolio level over a certain time period but may be performance-based to some degree. For example, if a drug is successful, then extra funding may be available for future drugs. This kind of dynamic budget may be naturally incorporated within the portfolio problem, and poses no problems for the dynamic programming method based on the budget remaining state space.

Applications in specialist settings

The portfolio problem applies when there is a pipeline of drugs which are available over time with degrees of uncertainty attached. When this is the case, the portfolio problem may be used to provide a statistical model. In the case of basket trials (Hirakawa et al. (2018)), a single targeted therapy is used to target different diseases or multiple disease sub-types; for example, on a single mutation on a range of tumour types. A complication is that these trials may have drugs from different sponsors.

This could potentially be modelled using the portfolio problem if we assume that the efficacy of the treatment for any two diseases are independent, and each disease area is available to start the trial at a particular point in time in the future with particular probability.

7 Optimal Group Sequential Designs

7.1 Introduction

We introduced group sequential designs in Chapter 2, where we noted the ethical, administrative, and economic benefits to a trial sponsor. In Chapters 3, 5, and 6, we use group sequential designs in simulation studies and highlight the benefit they can bring to a programme or portfolio in drug development. In each of these applications, popular designs such as ρ-family error spending group sequential designs or the Pampollona and Tsiatis family (see Pampallona and Tsiatis (1994)) are used.

In this chapter we discuss the boundaries of a group sequential design and extend the theory of optimal asymmetric one-sided group sequential designs to a general gain function. These group sequential designs will have boundaries that perform more efficiently than those determined parametrically such as the ρ-family error spending and the Pampollona and Tsiatis designs.

7.1.1 Optimal group sequential designs

The choice of group sequential design to choose for a study involves a few considerations. These include the simplicity of the design (in order to explain the design to stakeholders), the flexibility of the design (such as allowing the analyses to take place at information levels which are not predetermined), and the efficiency under assumptions about the treatment effect (such as the expected sample size).

In Barber and Jennison (2002), the authors extend the method used by Eales and Jennison (1992) to find optimal symmetric group sequential tests to optimise over a larger class than symmetric designs. Barber and Jennison show how one sided group sequential tests with non-equal type I and II error rates can be made optimal in the sense of minimising the expected sample size over different assumptions about the treatment effect. In particular, the authors give a method to solve the following problem:

Find acceptance $a_1, ..., a_K$ and rejection $b_1, ..., b_K$ boundaries such that

$$\frac{1}{2}(\mathbb{E}_0(N) + \mathbb{E}_\delta(N)) \tag{7.1}$$

is minimised, subject to the group sequential design having type I error α, and type II error β at $\theta = \delta$, where $\mathbb{E}_\theta(N)$ is the expected sample size of the group sequential design when the

treatment effect is θ.

In the Barber and Jennison paper, a Lagrangian Multiplier approach is used to find the optimal group sequential designs. A new objective function is defined by adding the cost of an incorrect decision to the original gain function. The cost of an incorrect decision is represented by constants d_0 and d_δ, associated with the cost of a type I and II error respectively. The optimal group sequential design is found using this new objective function for the unconstrained problem which does not impose the type I and II error conditions. This solution is the Bayes optimal design for the unconstrained Bayes optimal design problem. One then performs a search over d_0 and d_δ until the solution of this problem has the desired type I and II error rates. The optimal group sequential design for the unconstrained problem with those d_0 and d_δ is then the optimal group sequential design for the constrained problem with the original gain function given the specified type I and II error rate constraints.

In this chapter, we show how to generalise this approach to construct optimal group sequential designs that maximise a general financial model gain function that may more accurately model the financial aspects of the trial. In Barber and Jennison (2002), the rho-family error spending designs are found to be close to optimal. We shall look at whether these designs are still close to optimal for our financial model gain function.

7.2 Optimal group sequential design theory

7.2.1 Canonical distribution results

From Jennison and Turnbull (2000), the Z-statistics in a group sequential trial follow a canonical distribution. Denote by n_k the sample size (per treatment) at analysis k for $k = 1, ..., K$. We assume the same model as in Chapter 3. In particular, we equally allocate patients to treatment and control and assume responses are normally distributed with known variance σ^2 and with different means. Treatment effect θ is defined as the difference between the mean of treatment responses minus the mean of control responses. Denote ϕ as the probability density function of the standard normal distribution.

We describe results that follow from the following two properties of the canonical distribution described in Section 2.3.2, using the fact that in this setting, the information level at stage k is equal to $\mathcal{I}_k = n_k/(2\sigma^2)$ (see Chapter 3 Jennison and Turnbull (2000) for details):

- $Z_1 \sim N(\theta\sqrt{\frac{n_1}{2\sigma^2}}, 1)$

The probability density function of Z_1 given θ is

$$p_\theta(z_1) = \phi\left(z_1 - \theta\sqrt{\frac{n_1}{2\sigma^2}}\right)$$

with probabilities of rejection and acceptance at stage 1 of

$$\begin{aligned} P_\theta(Z_1 > b_1) =& 1 - \Phi\left(b_1 - \theta\sqrt{\frac{n_1}{2\sigma^2}}\right) \\ P_\theta(Z_1 < a_1) =& \Phi\left(a_1 - \theta\sqrt{\frac{n_1}{2\sigma^2}}\right). \end{aligned}$$

Secondly, we let $\mu_{\theta,k}(z_k)$ and ν_k denote

$$\begin{aligned}\mu_{\theta,k}(z_k) :=& z_k\sqrt{\frac{n_k}{n_{k+1}}} + \frac{\theta}{\sqrt{2}\sigma}\left(\frac{n_{k+1}-n_k}{\sqrt{n_{k+1}}}\right)\\ \nu_k^2 :=& \frac{n_{k+1}-n_k}{n_{k+1}}\end{aligned}$$

- $Z_{k+1}|Z_k = z_k \sim N(\mu_{\theta,k}(z_k), \nu_k^2)$ for $1 \leq k \leq K-1$

The probability density function of z_{k+1} given z_k and θ is

$$p_\theta(z_{k+1}; z_k) = \frac{1}{\nu_k}\phi\left(\frac{z_{k+1}-\mu_{\theta,k}(z_k)}{\nu_k}\right)$$

with probabilities of rejection and acceptance at stage $k+1$ of

$$\begin{aligned}P_\theta(z_{k+1} > b_{k+1}; z_k) =& 1 - \Phi\left(\frac{b_{k+1}-\mu_{\theta,k}(z_k)}{\nu_k}\right)\\ P_\theta(z_{k+1} < a_{k+1}; z_k) =& \Phi\left(\frac{a_{k+1}-\mu_{\theta,k}(z_k)}{\nu_k}\right),\end{aligned}$$

7.2.2 Case A: Gain function does not explicitly depend on θ

In this section, we outline the method for constructing optimal group sequential designs in the case when the gain function does not depend on θ. We define the gain function $\mathcal{G}(k, R)$ as the gain incurred by a group sequential trial that stops at stage k for rejection $R = 1$ or acceptance $R = 0$. One envisages this gain function to be much larger when $R = 1$ than $R = 0$ and decreasing in k representing the increasing number of patients required to be treated and the less time one has until patent expiry. As in Barber and Jennison (2002), we formulate the problem as an unconstrained Bayes problem with an objective function and use Langrangian Multiplier arguments to find the solution to the overall frequentist problem.

Overall Frequentist Problem

Suppose the group sequential design has K analyses, equally spaced on the information scale, and final information level $\mathcal{I}_{max} = R\,\mathcal{I}_{fix}$ for treatment and control where $R > 1$ is the ratio between the final information level and the information level required for a fixed sample design $\mathcal{I}_{fix}$. That is,

$$\mathcal{I}_{fix} = (\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta))^2/\delta^2. \tag{7.2}$$

We wish to find acceptance and rejection boundaries $a_1, ..., a_K, b_1, ..., b_K$ that maximise the expected value of $\int_{\mathbb{R}} \mathbb{E}_\theta[\mathcal{G}(k, R)]\ \pi_\theta(\theta)\ d\theta$ over all boundaries which give type I error rates of α and powers of $1-\beta$ when $\theta = \delta$.

We suppose π_θ is of the form

$$\pi_\theta(\theta) = \begin{cases}\pi_1 & \theta = \delta\\ 1-\pi_1 & \theta = 0\end{cases}. \tag{7.3}$$

Below, we describe the details of the Bayes formulation.

Prior and posterior distributions

Given Equation 7.3 defines the prior distribution on θ, the posterior distribution of θ given data summarised by Z-statistic $Z = z_k$ at stage k has probability density function

$$\begin{aligned} p^{(k)}(\theta; z_k) =& C\ \pi(z_k|\theta)\ \pi_\theta(\theta) \\ =& C \begin{cases} \pi_1\ \phi(z_k - \delta\frac{\sqrt{n_k}}{2\sigma}) & \theta = \delta \\ (1-\pi_1)\ \phi(z_k) & \theta = 0. \end{cases} \end{aligned}$$

Lagrangian Objective function

Define the objective function $\mathcal{OF}$ as

$$\mathcal{OF} := \mathcal{G}(k, R) - \lambda_1 \mathbb{1}_{(\text{reject},\theta=0)} - \lambda_2 \mathbb{1}_{(\text{accept},\theta=\delta)}, \tag{7.4}$$

where $\mathbb{1}_{(\text{reject},\theta=0)}$ is the indicator function that one rejects the null hypothesis when $\theta = 0$, and $\mathbb{1}_{(\text{accept},\theta=\delta)}$ is similarly defined. The unconstrained Bayes problem is to find $a_1, ..., a_K, b_1, ..., b_K$ such that the expected value of $\mathcal{OF}$ is maximised under prior π_θ. The solution of this unconstrained problem (that is, without type I and II error rate constraints) solves the original frequentist problem when λ_1 and λ_2 are such that the solution to the Bayes problem has the required Type I and II error constraints.

Conditional expected gain given Z_k

Suppose at stage k ($1 \le k \le K-1$), one has a Z-statistic of z_k. Then the conditional expected gain given $Z_k = z_k$ is

$$\mathbb{E}_{z_k}[\mathcal{OF}] = A(z_k)\mathbb{1}_{(z_k > b_k)} + B(z_k)\mathbb{1}_{(z_k < a_k)} + C(z_k)\mathbb{1}_{(a_k < z_k < b_k)}, \tag{7.5}$$

where

$$\begin{aligned} A(z_k) &= \mathcal{G}(k, R=1) - \lambda_1 p^{(k)}(0; z_k) \\ B(z_k) &= \mathcal{G}(k, R=0) - \lambda_2 p^{(k)}(\delta; z_k) \\ C(z_k) &= \int_{-\infty}^{\infty} [p_0(z_{k+1}; z_k)\ p^{(k)}(0; z_k) + p_\delta(z_{k+1}; z_k)\ p^{(k)}(\delta; z_k)]\ \mathbb{E}_{z_{k+1}}[\mathcal{OF}]\ dz_{k+1}. \end{aligned} \tag{7.6}$$

When $k = K$, we have the same expression but without the third term. $A(z_k)$, $B(z_k)$, and $C(z_k)$ represent the expected value of the objective function when one stops for rejection, stops for acceptance, or continues at stage k, given one has observed z_k. $A(z_k)$ and $B(z_k)$ are easily computed. We split up $C(z_k)$ into two parts by conditioning on z_{k+1}, the Z-statistic from stage $k+1$, in the cases when one stops at stage $k+1$ for acceptance or rejection, or one falls in the continuation region of stage $k+1$. Thus

$$C(z_k) = C_1(z_k) + C_2(z_k), \text{ where} \tag{7.7}$$

$$
\begin{aligned}
C_1(z_k) = & \int_{b_{k+1}}^{\infty} p_0(z_{k+1}; z_k)\ [\mathcal{G}(k+1, R=1) - \lambda_1]\ dz_{k+1}\ p^{(k)}(0; z_k)\ + \\
& \int_{b_{k+1}}^{\infty} p_\delta(z_{k+1}; z_k)\ \mathcal{G}(k+1, R=1)\ dz_{k+1}\ p^{(k)}(\delta; z_k)\ + \\
& \int_{-\infty}^{a_{k+1}} p_0(z_{k+1}; z_k)\ \mathcal{G}(k+1, R=0)\ dz_{k+1}\ p^{(k)}(0; z_k)\ + \\
& \int_{-\infty}^{a_{k+1}} p_0(z_{k+1}; z_k)\ [\mathcal{G}(k+1, R=0) - \lambda_2]\ dz_{k+1}\ p^{(k)}(\delta; z_k) \\
= & \left(1 - \Phi\left(\frac{b_{k+1} - \mu_0}{\sigma}\right)\right)\ [\mathcal{G}(k+1, R=1) - \lambda_1]\ p^{(k)}(0; z_k)\ + \\
& \left(1 - \Phi\left(\frac{b_{k+1} - \mu_\delta}{\sigma}\right)\right)\ \mathcal{G}(k+1, R=1)\ p^{(k)}(\delta; z_k)\ + \\
& \Phi\left(\frac{a_{k+1} - \mu_0}{\sigma}\right)\ \mathcal{G}(k+1, R=0)\ p^{(k)}(0; z_k)\ + \\
& \Phi\left(\frac{a_{k+1} - \mu_\delta}{\sigma}\right)\ [\mathcal{G}(k+1, R=0) - \lambda_2]\ p^{(k)}(\delta; z_k),
\end{aligned}
\tag{7.8}
$$

where $\mu_{\theta,k}(z_k)$, and σ are defined before. This is now in an easily computable form.

$$
\begin{aligned}
C_2(z_k) = & \int_{a_{k+1}}^{b_{k+1}} (\ p_0(z_{k+1}; z_k) p^{(k)}(0; z_k) + p_\delta(z_{k+1}, z_k) p^{(k)}(\delta; z_k)\ )\ \mathbb{E}_{z_{k+1}}\ [\mathcal{OF}]\ dz_{k+1} \\
= & \int_{a_{k+1}}^{b_{k+1}} \frac{1}{\sigma}\phi\left(\frac{z_{k+1} - \mu_0}{\sigma}\right)\ \mathbb{E}_{z_{k+1}}[\mathcal{OF}]\ dz_{k+1}\ p^{(k)}(0; z_k)\ + \\
& \int_{a_{k+1}}^{b_{k+1}} \frac{1}{\sigma}\phi\left(\frac{z_{k+1} - \mu_\delta}{\sigma}\right)\ \mathbb{E}_{z_{k+1}}[\mathcal{OF}]\ dz_{k+1}\ p^{(k)}(\delta; z_k).
\end{aligned}
\tag{7.9}
$$

This form requires integrating over the continuation region of stage $k+1$. Thus to compute this, we must have evaluations of $\mathbb{E}_{z_{k+1}}[\mathcal{OF}]$ for a finite number of points within $z_{k+1} \in [a_{k+1}, b_{k+1}]$.

In Section 7.3, we outline the computations required to use these integrals to compute the optimal group sequential designs.

7.2.3 Case B: Gain function may explicitly depend on θ

In this section we generalise the methods of the previous section and consider the case where the gain function may depend explicitly in terms of θ. Denote the gain function as $\mathcal{G}(k, \theta, R)$. We have the same overall frequentist problem as Case A but we wish to maximise the expected value of $\int_{\mathbb{R}} \mathbb{E}_\theta[\mathcal{G}(k, \theta, R)]\ \pi_G(\theta)\ d\theta$ over all boundaries which give type I error rates of α and powers of $1 - \beta$ when $\theta = \delta$, where we suppose π_G is the probability density function of a Gaussian distribution.

Prior and posterior distributions

This time we require a hybrid continuous and discrete prior. We require a discrete element to the prior in addition to π_G to use the Lagrangian Multiplier argument to derive the optimal group sequential design.

Therefore we define the prior as

$$\pi_\theta(\theta) = \begin{cases} 1/3 & \theta = 0 \\ 1/3 & \theta = \delta \\ 1/3 & \theta \sim \pi_G(\theta) \end{cases} \tag{7.10}$$

for some $\epsilon > 0$.

Let E_1, E_2, E_3 be 3 events defined in the above prior. The posterior distributions are as follows:

$$\begin{aligned} \mathbb{P}(E_1|z_k) &= p_0(z_k) \ / \ (3\pi_Z(z_k)) \\ \mathbb{P}(E_2|z_k) &= p_\delta(z_k) \ / \ (3\pi_Z(z_k)) \\ \mathbb{P}(E_3|z_k) &= \int_\theta p_\theta(z_k) \ \pi_G(\theta) \ d\theta \ / \ (3\pi_Z(z_k)) \end{aligned} \tag{7.11}$$

where $\pi_Z(z_k)$ is the marginal probability density function of observing the Z-statistic z_k and may be deduced trivially by using the relation $\mathbb{P}(E_1|z_k) + \mathbb{P}(E_2|z_k) + \mathbb{P}(E_3|z_k) = 1$. The posterior distribution of θ given z_k under event E_3 may be written as

$$\pi_{E_3}(\theta|z_k) = \frac{p_\theta(z_k) \ \pi_G(\theta)}{\int p_\theta(z_k)\pi_G(\theta)d\theta}. \tag{7.12}$$

Lagrangian Objective function

This time the gain function may depend upon the treatment effect θ. Let $\mathcal{G}(k, \theta, R)$ denote the gain incurred by a group sequential trial that stops at stage k for rejection $R = 1$ or acceptance $R = 0$, when the treatment effect is θ. Define the objective function $\mathcal{OF}$ as

$$\mathcal{OF} := 3\mathcal{G}(k, \theta, R)\mathbb{1}_{(\theta \in \mathbb{R} \setminus \{0,\delta\})} - \lambda_1 \mathbb{1}_{(\text{reject},\theta=0)} - \lambda_2 \mathbb{1}_{(\text{accept},\theta=\delta)} \tag{7.13}$$

with the same notation as before. The unconstrained Bayes problem mirrors the one of Case A.

Conditional expected gain given Z_k

Suppose at stage k (for $1 \leq k \leq K-1$), one has a Z-statistic of z_k. Then the conditional expected gain given $Z_k = z_k$ is

$$\begin{aligned} \mathbb{E}_{z_k}[\mathcal{OF}] = & \left[\int_{\mathbb{R}} \pi_{E_3}(\theta|z_k) \ \mathcal{G}(k, \theta, R = 1) \ d\theta \ 3\mathbb{P}(E_3|z_k) - \lambda_1 \mathbb{P}(E_1|z_k) \right] \mathbb{1}_{(z_k > b_k)} \\ & + \left[\int_{\mathbb{R}} \pi_{E_3}(\theta|z_k) \ \mathcal{G}(k, \theta, R = 0) \ d\theta \ 3\mathbb{P}(E_3|z_k) - \lambda_2 \mathbb{P}(E_2|z_k) \right] \mathbb{1}_{(z_k < a_k)} \\ & + \int_{\mathbb{R}} \Big(\int_{\mathbb{R}} p_\theta(z_{k+1}; z_k) \ \pi_{E_3}(\theta|z_k) \ d\theta \ 3\mathbb{P}(E_3; z_k) + p_\delta(z_{k+1}; z_k) \ \mathbb{P}(E_2; z_k) \\ & \qquad + p_0(z_{k+1}; z_k) \ \mathbb{P}(E_1; z_k) \Big) \ \mathbb{E}_{z_{k+1}}[\mathcal{OF}] \ dz_{k+1} \ \mathbb{1}_{(a_k < z_k < b_k)}, \end{aligned} \tag{7.14}$$

where as before the $k = K$ case has no third term.

As before in Case A, we write

$$\mathbb{E}_{z_k}[\mathcal{OF}] = A(z_k)\mathbb{1}_{(z_k > b_k)} + B(z_k)\mathbb{1}_{(z_k < a_k)} + C(z_k)\mathbb{1}_{(a_k < z_k < b_k)} \tag{7.15}$$

and use numerical integration routines to evaluate each of $A(z_k)$, $B(z_k)$, and $C(z_k)$. Due to the dependence upon θ, each of these are more computationally expensive than Case A.

In Section 7.3, we outline the computations required to use these integrals to compute the optimal group sequential designs.

7.3 Computations

In this section, we outline the dynamic programming algorithms that may be used to construct the optimal group sequential designs.

7.3.1 Optimal decisions

The group sequential designs are optimal in the sense that the rejection and acceptance boundaries $\boldsymbol{a} = (a_1, ..., a_K)$ and $\boldsymbol{b} = (b_1, ..., b_K)$ are chosen such that the expected value of the gain function is maximised.

To do this, we assume the number of analyses K is fixed, and the inflation factor R of the total group sequential design sample size over fixed sample sample size is fixed (one may search over different values of R afterwards if desired). The type I error α, and type II error β at $\theta = \delta$ are specified.

Denoting the information required for a fixed sample design with type I error α and type II error β as $\mathcal{I}_{fix}$, we have the standard result,

$$\mathcal{I}_{fix} = (\Phi^{-1}(1-\alpha) + \Phi^{-1}(1-\beta))^2/\delta^2. \tag{7.16}$$

The analyses are then performed at information levels

$$\boldsymbol{\mathcal{I}} = (\mathcal{I}_1, ..., \mathcal{I}_K) \text{ where } \mathcal{I}_k = R\mathcal{I}_{fix}\frac{k}{K} \text{ for } k = 1, ..., K. \tag{7.17}$$

Optimal decision at analysis $k = K$

Suppose one is at analysis $k = K$ with Z-statistic z_K. One wishes to maximise the expected value of the objective function for any z_K. Therefore, to find the value of a_K $(= b_K)$, we find the z_K such that

$$A(z_K) = B(z_K) \tag{7.18}$$

where these functions are defined in Equations 7.5 or 7.15. This is our final rejection and acceptance boundary point $a_K = b_K$.

Optimal decision at analysis $k = 1, ..., K-1$

Likewise, suppose one is at analysis $k < K$ with Z-statistic z_k. We find b_k by finding the z_k such that

$$A(z_k) = C(z_k), \tag{7.19}$$

and a_k by finding the z_k such that

$$B(z_k) = C(z_k), \tag{7.20}$$

where these functions are again defined in Equations 7.5 or 7.15. This gives us our acceptance a_k and rejection b_k boundary points at stage k.

7.3.2 Dynamic programming algorithms

In the algorithm below, we outline how to calculate an optimal group sequential design.

`Construct_OptGSD_lambda12_func`

- Compute information levels $\boldsymbol{\mathcal{I}}$ from Equation 7.17.
- Find final boundary $a_K = b_K$ by solving Equation 7.18.
- Find penultimate acceptance a_{K-1} and rejection b_{K-1} boundaries by solving Equations 7.19 and 7.20.
- For $k = K-2, ..., 1$
  - Create a finite mesh vector $\mathcal{M}_{k+1}$ of equally spaced points in the interval (a_{k+1}, b_{k+1}).
  - For each $z_{k+1} \in \mathcal{M}_{k+1}$, calculate and store $C(z_{k+1})$ from Equation 7.5 (Case A) or 7.15 (Case B).
  - Find acceptance a_k and rejection b_k boundaries by solving Equations 7.19 and 7.20, using the stored mesh of points $\mathcal{M}_{k+1}$ and corresponding values of $C(z_{k_1})$ at analysis $k+1$ to aid the numerical integration.
- Calculate the probability of acceptance and rejection under $\theta = 0$ (denoting as p_0^{acc}, p_0^{rej}) and $\theta = \delta$ (denoting as $p_\delta^{acc}, p_\delta^{rej}$) using standard techniques (see Jennison and Turnbull (2000)).
- Return $\boldsymbol{\mathcal{I}}$, $\boldsymbol{a}, \boldsymbol{b}$, and $p_0^{acc}, p_0^{rej}, p_\delta^{acc}, p_\delta^{rej}$.

`Construct_OptGSD_func`

- Perform a 2 dimensional search over λ_1 and λ_2 until `Construct_OptGSD_lambda12_func` outputs a value of p_0^{rej} equal to α and p_δ^{rej} equal to β.
- Return all the properties of the group sequential design that satisfies this, including the expected value of the original gain function. By the Lagrangian Multiplier principle, this group sequential design is optimal (has the highest expected gain) over all boundaries such that the type I error and power are α and β respectively.

7.4 Comparing group sequential design performances under the financial model

In this section, we compare the performance of non optimal group sequential designs against our optimal design. Group sequential designs are commonly parameterised by one or two parameters, so we compare the performance of these group sequential designs using commonly used parameter values. We then examine how the parameter selection can improve the performance of each group sequential design, and identify how close one can get to the optimal group sequential design.

We use the Financial Model from Chapter 6 as our gain function, with parameters corresponding to Drug 1.

7.4.1 Efficiency of the error spending and Pampallona and Tsiatis designs

In Chapter 2, we introduced the one sided ρ-family error spending group sequential design family and the Pampallona and Tsiatis group sequential Δ-family designs. The error spending family is parameterised by ρ_1 and ρ_2, and the Pampallona and Tsiatis family is parameterised by Δ. In previous simulations studies, we have used the parameters $\rho_1 = \rho_2 = 2$ and $\Delta = 0.25$ for these choice of parameters.

Below, we compare these two group sequential designs with the optimal group sequential design under the financial model from Chapter 6 Case Study 1. We do this firstly with the usual parameters values for ρ_1, ρ_2, and Δ, and then we tune the parameter values to obtain the best designs possible under our financial model.

All group sequential designs are specified to have 5 interim analyses, and type I error 0.05 and power 0.8 at $\theta = 1$, and using the Drug 1 Financial Model parameters from the simulation study in Section 6.7.1. The optimal GSD is optimised over inflation factor R also. For the Error Spending and Pampallona and Tsiatis group sequential designs, the final information level is a function of the parameter values. In Table 7.1, we list the expected gain of these different GSDs with different parameter values, and plot the corresponding GSDs in Figure 7-1.

Table 7.1: The expected gain of the optimal, Error Spending, and Pampallona Tsiatis GSDs under different parameter values.

GSD	**Parameter Values**	**Expected Gain**
Optimal GSD	none	3 920
Error Spending GSD	$\rho_1 = \rho_2 = 2$	3 834
	$\rho_1 = 0.59, \rho_2 = 5.76$	3 913
Pampallona Tsiatis GSD	$\Delta = 0.25$	3 827
	$\Delta = 0.43$	3 844

From these results, one can see that both designs are not much worse than the optimal design, especially when their parameters are optimised. In particular, the Error Spending design comes very close to optimal and its shape very closely matched the optimal group sequential design. The Pampallona and Tsiatis design we study here has only one parameter, so the effect of optimising this parameter is less pronounced.

The use of the Financial Model suggests it is more important to stop early for efficacy at the expense of stopping early for futility and the final information level.

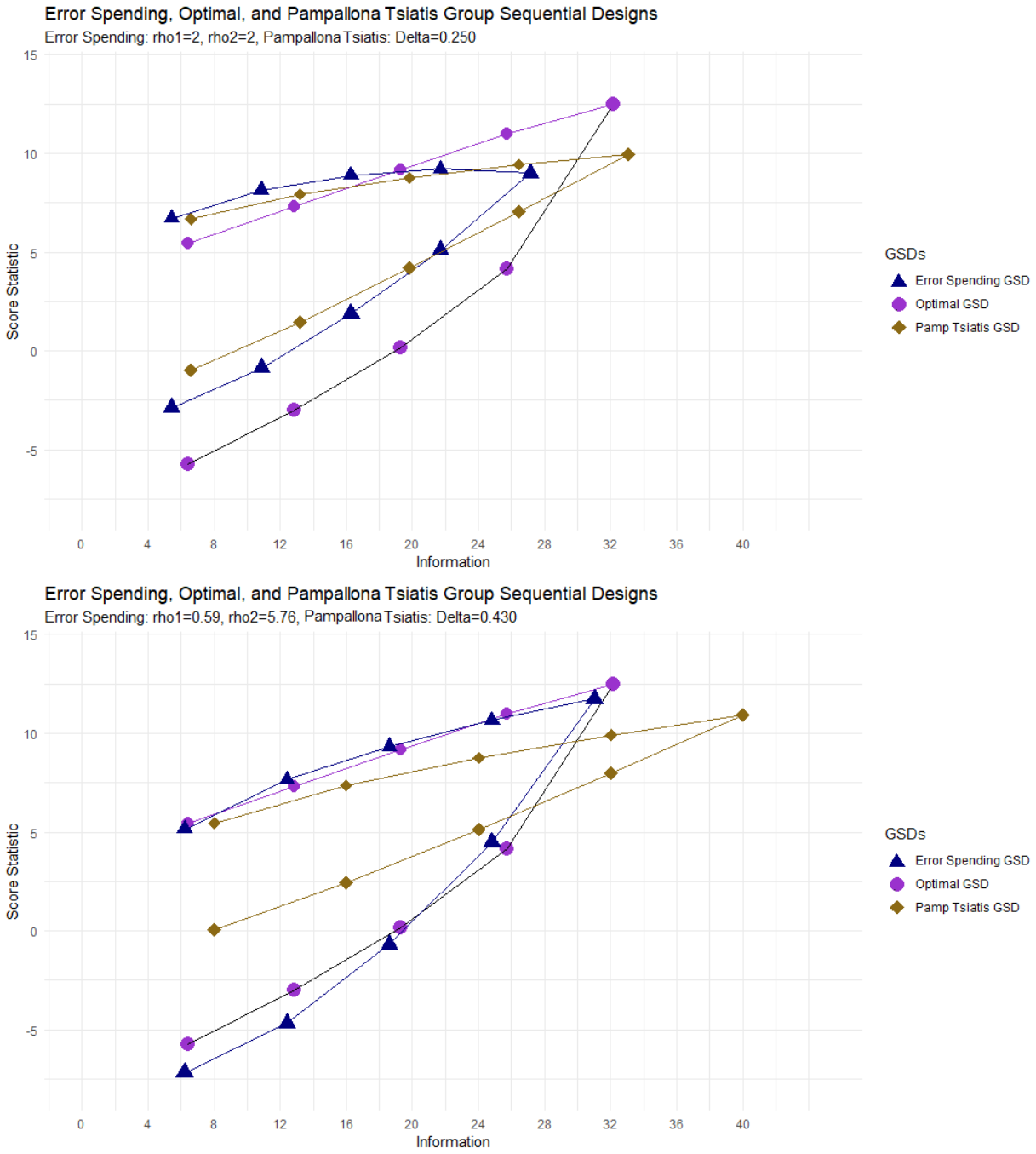

Figure 7-1: Error Spending, Optimal, and Pampallona Tsiatis group sequential designs as computed in Table 7.1. The top figure gives the group sequential designs for the usual parameter values, and the bottom for the parameter values that maximise the value of the design under the financial model.

7.5 Discussion

In this chapter, we outlined a method to construct optimal designs according to some general gain function and under a prior on treatment effect θ, extending the work of Barber and Jennison (2002). In particular, optimal designs can be constructed to maximise the eNPV when the gain function used is the Financial Model gain function introduced in Chapter 1 and used in Chapters 3 and 6.

When comparing the optimal designs to commonly used designs such as one sided ρ-family

Error Spending designs and Pampallona and Tsiatis Δ-family designs, the difference in performance was not too large in the example considered.

Reasons for not using this approach may stem from being critical of the use of a Financial Model decision theory approach for single Phase III trials only and thus missing the bigger picture with respect to the opportunity cost of investing resources too heavily in a single trial. It is also the case that parameters in the Financial Model that may affect the design are hard to estimate well; for example, the revenue per month if the drug passes Phase III.

8 Thesis Overview

8.1 Decision making in drug development

The pharmaceutical industry has a moral duty to develop treatments to satisfy an unmet medical need. This may be where there are no satisfactory treatments, or the current treatment can be improved upon. The industry has come to an era where there is an increasing amount of pressure for sponsors to be cost-effective and efficient in their drug development strategies due to increasing costs and diminishing returns.

The lack of uptake in quantitative methods that support decision making processes contribute to a lack of efficiency. Utilisation of decision analysis, statistical resources, and modelling and simulation are methods that allow one to make more informed decisions in order to increase the efficiency of drug development.

In this thesis, we have examined a range of scenarios in drug development where quantitative methods can aid decision making. One only has to consider a simple scenario of a few drugs with some information about their efficacy under uncertainty, before decisions about the future development of these drugs becomes a complex problem with trade-offs between different decisions. These complex decisions have large financial implications and are prone to cognitive bias. The approach taken in this thesis is to utilise decision theory in order to gain insight into the problem. Bayesian methods may naturally be used when there is uncertainty attached to certain beliefs and one may obtain information throughout the process that may inform decision making later in the process.

In the following section we outline the scenarios studied in this thesis, the methods required to gain insight into the problem using decision theory, and the insights gained in case studies. We then discuss the overall themes pertaining to this thesis, and outline extensions that have arisen.

8.2 Summary of results

8.2.1 The value of adaptivity in a Phase II/III programme with treatment selection (Chapter 3)

We consider a Phase II/III drug development programme which contains multiple treatments entering Phase II where one treatment is selected to proceed to Phase III given the data from Phase II. The sample sizes of Phase II and III must be specified during the programme.

In this programme, one defines two decision points before Phase II and Phase III when the decisions are made. Bayesian decision theory is used to derive optimal decision rules using a gain function for each decision point using information about the treatment effects of the treatments under uncertainty. In the first decision point before Phase II, this information is a continuous prior distribution on the treatment effects. In the second decision point before Phase III, this decision may be informed by the Phase II data which is combined with the prior distribution according to Bayesian principles. The optimal decisions may be computed using numerical integration and simulation techniques. In particular, Monte Carlo integration is used in the first decision point and is computationally expensive when the programme contains adaptive elements such as group sequential methods.

Applying these methods to a case study, it is found one can compute optimal decision rules for both decision points and infer the value of the programme. One can specify the gain function to be a simple function that rewards rejecting the null hypothesis of a working treatment in Phase III, or a more complex function that more accurately models the net present value of a programme. It is found that adding adaptive elements to the programme in the form of combination tests or group sequential methods brings added value to the programme and changes the optimal decision rules. Group sequential methods are found to bring comparatively more value to the programme than combination tests.

8.2.2 The value of dose response modelling in Phase II/III programmes (Chapter 4)

A Phase II/III drug development programme is considered in which multiple doses of the same treatment are tested in Phase II with one dose selected to proceed to Phase III given data from Phase II. Dose response modelling techniques may be used on the Phase II data to inform decision making. As before, the sample sizes of Phase II and III must be specified during the programme.

Bayesian decision theory is used to derive optimal decision rules for decision points before Phase II and III using a gain function. One assumes that the efficacy of larger doses is expected to be larger, but this comes at the cost of a safety penalty, representing the risk of failure of the treatment due to safety concerns. Dose response modelling procedures may involve fitting parametric models to model the efficacy, or using procedures such as MCP-Mod (Bornkamp (2006)).

The use of dose response relationships to aid decision making add value to the programme when the doses and efficacy responses follow some dose response relationship in comparison to making decisions under the assumption the doses are independent treatments. When there is uncertainty as to the true dose response relationship, a flexible procedure such as MCP-Mod adds value to the programme as it is able to use the most appropriate dose response model that best fits the observed data in order to make inferences for decision making.

8.2.3 Multiple Phase IIIs (Chapter 5)

Regulations often require the use of two independent Phase III trials in order to gain market approval for a new treatment. We consider the best way to perform these two trials; in parallel, sequentially, or in an adaptive procedure starting the second halfway through the

first. Furthermore, if these trials are group sequential, one can ask what is the best family of acceptance and rejection bounds.

We formulate these problems mathematically, identify the decision points, and compute optimal decision rules using Bayesian decision theory. The choice between parallel and sequential trials becomes a trade off between completing both trials earlier to realise more marketing time before patent expiry, or to reduce unnecessary patient costs by using initial results from the first trial to inform whether performing the second trial is worthwhile.

It is found that the prior information about the drug's efficacy and the financial parameters determine the best way to perform the two Phase III trials. An adaptive compromise between sequential and parallel design adds value over the two alternatives in some situations.

8.2.4 The portfolio problem (Chapter 6)

We consider a portfolio of treatments which are approaching Phase III in the drug development process in the near future, but have some probability of failure before reaching Phase III. A budget is available for the entire portfolio meaning decisions about the investment for each treatment depend upon the other treatments. We require an optimal design strategy that allocates the budget to the treatments within the portfolio in order to maximise the portfolio value.

The optimal design strategy is found by finding the optimal decision rules at each treatment given the current status of the remaining budget and ongoing trials. These optimal decision rules are derived using dynamic programming as an alternative to the method of Stochastic Integer Programming used in Patel et al. (2013). The dynamic programming method is more efficient, and allows the use of group sequential designs within the portfolio.

A realistic portfolio of fixed sample Phase III designs is used as a case study and optimal designs are found for each treatment. Adding group sequential designs adds value to the portfolio, even when a minimum sample size is required to obtain a sufficient amount of data for safety purposes. However, adding group sequential designs to the portfolio increases the computational workload of the dynamic programming algorithm. Another case study found that the presence of drugs under development from other sponsors that may become competitors meant it became optimal to invest less in those drugs with possible competitors.

8.2.5 Optimal group sequential designs (Chapter 7)

Group Sequential Designs often have boundaries specified by parametric functions. Barber and Jennison (2002) provides an approach to instead find optimal boundaries to minimise the expected sample size under assumptions about the treatment effect given a specified type I error rate and power. We generalise this approach to find optimal boundaries which maximise a general gain function.

Using Lagrangian Multiplier arguments, we formulate this optimisation problem as a Bayesian decision theory problem. We use dynamic programming to derive the optimal boundaries at each stage in the group sequential design.

An algorithm is derived which may be used to derive these optimal group sequential designs. Using a gain function representing the financial aspects of the trial gives boundaries that

prioritise early stopping for efficacy rather than for futility in order to maximise the time the drug can be marketed until patent expiry.

8.3 Discussion points

8.3.1 Decision theory as a quantitative method for aiding decision making

There are numerous factors that are important when planning pharmaceutical programmes or portfolios. These may be economic, statistical, and logistical. Decisions regarding different development options should be taken such that the expected value of the development programme or portfolio is maximised. Decision theory is a tool which can help quantify these values.

Optimisation can be done at an individual trial level, programme level, or portfolio level. What is optimal at one level may not be optimal at a higher level as individual trials and programmes may be interdependent- for example, due to a shared research and development budget. However, the complexity of the model may mean that only simple decisions can be modelled at a higher level. Therefore one is left with a trade off between the ability to more accurately model complex decisions, and to keep the bigger picture in mind. It is useful to work at all levels in order to obtain an appreciation of the trade-offs between different decisions.

The value of a programme or portfolio depends upon the quality of the product, associated beliefs about the treatment effect of the product, and the development strategy. Decision theory can inform the development strategy and thus has the potential to increase the value of a programme or portfolio within drug development. This is due to

- more efficient allocation of budget to individual trials or treatments,
- more efficient choices of dose or sample size for individual trials, and
- providing evidence of the benefit of adaptive designs.

All of the case studies within this thesis use gain functions which aim to model the financial aspects of the programme or portfolio. These may be simple functions, or more complex functions which aim to more accurately model the financial aspects. The financial aspects are modelled using the concepts of net present value. Decisions are made under uncertainty and therefore a common measure to use is the expected net present value. In this thesis, we have shown this measure naturally accommodates optimisation and fits harmoniously with Bayesian decision theory. The criticisms that have been noted with net present value relate to the setting in which the optimisation is performed. In many case studies, the cost of the drug development can become a small fraction of realised revenues. A small relative change in revenue in exchange for a larger development cost could therefore be considered justified given a net present value gain function. However, this may result in a large opportunity cost, where budget would have been better spent on other opportunities.

The method of decision theory depends on several assumptions. The gain function provides a measure which determines the relative importance of different outcomes to the sponsor. If the gain function is misspecified, then decisions which are optimal according to the gain function may not be satisfactory. However, specifying the gain function a-priori may be difficult. When the gain function aims to model the net present value of a programme or portfolio, we require the specification of parameters such as the revenue per month, which

may be difficult to estimate in advance. Furthermore, the net present value for a drug is highly dependent on the revenue per month. In some applications, such as in Chapter 7, a standard deviation is specified to allow for some uncertainty with this figure.

Obtaining optimal decision rules from case studies in this thesis relied on the rules being computationally solvable in a satisfactory time. In several case studies, we found that one may run into computational difficulties when the problem became too complex. Decision rules that are derived by Monte Carlo procedures are prone to having large computational expenditures, as a large number of simulations may be needed to obtain reliable estimates. Case studies in Chapter 3 and 4 require Monte Carlo estimates in Decision 1. One of the main motivators for a dynamic programming approach for the portfolio problem in Chapter 6 was that the currently used Stochastic Integer Programming method was particularly inefficient. We found that the dynamic programming method was more computationally efficient for large portfolios. However when many group sequential designs were added to the portfolio, the algorithm could become too computationally expensive to solve due to the number of values the group sequential design situation ID variable s in the state space could take.

It was necessary to use methods to ensure computational efficiency in the case studies in this thesis. When appropriate, computations were parallelised, and computations run with a high performance computing cluster with 16 cores.

8.3.2 The value of adaptive methods in drug development

In this thesis, we have principally studied two types of adaptive methods: group sequential designs and combination tests. Group sequential designs were studied in the context of Phase II/III programmes (Chapter 3), two Phase III trials (Chapter 5), Phase III portfolios (Chapter 6), and finding optimal group sequential designs (Chapter 7), whilst combination tests were studied in the context of Phase II/III programmes (Chapter 3).

In the context of Phase II/III programmes and Phase III portfolios, it was found there was a significant benefit to the sponsor if group sequential designs were used. As noted, this is due to the use of group sequential designs allowing trials to stop early for futility or efficacy. This means the drug can be marketed for longer until the patent expires and leftover budget is saved. It is found that the benefit of group sequential designs comes overwhelmingly from the longer marketing time rather than saving leftover budget. This comes from the gain function weighting the revenue much more highly than development costs.

As described in Chapter 2, combination tests introduce flexibility into clinical trials. The benefit of using combination tests to pool the data from multiple phases to increase the power of the hypothesis test is found to add value to Phase II/III Programmes (Chapter 3) but significantly less than using group sequential designs.

8.4 Extensions for future work

The case studies in this thesis have primarily been motivated by questions about the efficiency of traditional industrial practices. During investigations of these case studies, new questions have arisen. However due to the time constraints, not all of these new questions can be tackled. In this section, we outline some unanswered questions as extensions to the work done in this thesis. These extensions may inspire future work.

In Chapter 3, we assess the value of using combination tests in a Phase II/III portfolio. However, in Chapter 4, we focused on the value of dose response modelling in a Phase II/III programme with multiple doses of the same treatment. A question that arises is what is the value in using combination tests within a Phase II/III programme with multiple doses with dose response modelling following Phase II? Clearly, one cannot combine p-values that are found using dose response models as the overall combination test would then implicitly assume the dose response model was correct. However, a scheme where dose response models are used on the Phase II data to inform decisions about Phase III, and a combination test is performed on the Phase II and III data without any dose response model assumptions is possible and may add value.

In Chapter 5, we use two independent Phase III designs and allow them to be group sequential. Assuming the trials are done in parallel, one stops for futility if one of the trials stops for futility, and one stops for efficacy if both the trials have stopped for efficacy. Though the regulatory advice is that the trials should be independent, it is thought that sharing data between the trials when considering futility should not be problematic. One extension therefore is to investigate the efficiency of a pair of group sequential trials, where early stopping for efficacy for each trial depends upon the data for each trial separately, whilst early stopping for futility for each trial depends upon the pooled data from both trials.

When considering a portfolio in Chapter 6, we assume the efficacies of each of the treatments are independent of each other. That is, if one treatment is found to be efficacious, this does not affect the probability of another treatment being efficacious. Alternatively, the net present value of two treatments are the sum of the net present value of each of them; this may not be the case if there are two different treatments for the same medical condition. Using the method of dynamic programming may be difficult in this case, as the optimal decision for each drug will depend upon data about the efficacy of previous drugs, leading to a much larger state space. Therefore, to investigate this problem, one would have to use an alternative method to find the optimal decisions (such as Stochastic Integer Programming), or find a method for reducing the size of the state space.

In many case studies in this thesis, a gain function based on net present value is used to derive optimal decisions and we note that these decisions might not be optimal when we consider the larger problem (for example, a programme of many trials, or portfolio of many trials or programmes). One method for solving this problem would be to use a gain function which gives some measure of return ratio under some constraints. This is investigated briefly in Chapter 6 and in papers such as Chen et al. (2015). An extension of the work in this thesis would be to more thoroughly use these types of gain functions, to investigate the benefit of using decision rules derived from these gain functions in the bigger picture.

Bibliography

T. Aksamit, T.-J. Bandel, M. Criollo, A. De Soyza, J. S. Elborn, E. Operschall, E. Polverino, K. Roth, K. L. Winthrop, and R. Wilson. The RESPIRE trials: two Phase III, randomized, multicentre, placebo-controlled trials of ciprofloxacin dry powder for inhalation (ciprofloxacin dpi) in non-cystic fibrosis bronchiectasis. *Contemporary Clinical Crials*, 58: 78–85, 2017.

Z. Antonijevic. *Optimization of Pharmaceutical R&D Programs and Portfolios: Design and Investment Strategy*. Springer, 2014.

Z. Antonijevic. The impact of adaptive design on portfolio optimization. *Therapeutic Innovation & Regulatory Science*, 50(5):615–619, 2016.

Z. Antonijevic, J. Pinheiro, P. Fardipour, and R. J. Lewis. Impact of dose selection strategies used in Phase II on the probability of success in Phase III. *Statistics in Biopharmaceutical Research*, 2(4):469–486, 2010.

P. Armitage. Interim analyses in clinical trials. *Multiple Comparisons, Selection, and Applications in Biometry*, 134: 391–391, 1993.

S. Barber and C. Jennison. Optimal asymmetric one-sided group sequential tests. *Biometrika*, 89(1):49–60, 2002.

G. A. Barnard. Sequential tests in industrial statistics. *Supplement to the Journal of the Royal Statistical Society*, 8 (1):1–26, 1946.

P. Bauer and M. Kieser. Combining different phases in the development of medical treatments within a single trial. *Statistics in Medicine*, 18(14):1833–1848, 1999.

P. Bauer and K. Kohne. Evaluation of experiments with adaptive interim analyses. *Biometrics*, 50:1029–1041, 1994.

R. E. Bechhofer, J. Kiefer, and M. Sobel. *Sequential Identification and Ranking Procedures: with Special Reference to Koopman-Darmois Populations*. University of Chicago Press, 1968.

R. Bellman. *Dynamic Programming*. Courier Corporation, 1957.

J. O. Berger. *Statistical Decision Theory and Bayesian Analysis*. Springer Science & Business Media, 2013.

G. E. Blau, K. Rajan, J. F. Pekny, V. A. Varma, and P. M. Bunch. A genetic algorithm-based pharmaceutical portfolio selection and scheduling framework. *Proceedings Foundations of Computer-aided Process Operations 2003 (FOCAPO2003)*, 2003.

C. E. Bonferroni. *Statistical Class Theory and Calculation of Probabilities*. International Library Seeber, 1936.

F. L. Bookstein. Principal warps: Thin-plate splines and the decomposition of deformations. *IEEE Transactions on Pattern Analysis and Machine Intelligence*, 11(6):567–585, 1989.

B. Bornkamp. *Comparison of model-based and model-free approaches for the analysis of dose-response studies*. PhD thesis, Diplomarbeit, Fakultät Statistik, Technische Universität Dortmund, www. statistik. tu-dortmund. de/bornkamp/diplom. pdf, 2006.

B. Bornkamp and K. Ickstadt. Bayesian nonparametric estimation of continuous monotone functions with applications to dose–response analysis. *Biometrics*, 65(1):198–205, 2009.

B. Bornkamp, F. Bretz, A. Dmitrienko, G. Enas, B. Gaydos, C.-H. Hsu, F. König, M. Krams, Q. Liu, B. Neuenschwander, et al. Innovative approaches for designing and analyzing adaptive dose-ranging trials. *Journal of Biopharmaceutical Statistics*, 17(6):965–995, 2007.

B. Bornkamp, J. Pinheiro, and F. Bretz. Dosefinding: planning and analyzing dose finding experiments. *R package version 0.4-1*, 2010.

B. Bornkamp, J. Pinheiro, and F. Bretz. *DoseFinding*, 2017. R Package Manual, R package version 1.14.4.

F. Bretz and X. Xun. *Handbook of Methods for Designing Monitoring and Analyzing Dose-finding Trials*. Chapman and Hall, 2017.

F. Bretz, J. C. Pinheiro, and M. Branson. Combining multiple comparisons and modeling techniques in dose-response studies. *Biometrics*, 61(3):738–748, 2005.

F. Bretz, H. Schmidli, F. König, A. Racine, and W. Maurer. Confirmatory seamless Phase II/III clinical trials with hypotheses selection at interim: General concepts. *Biometrical Journal*, 48(4):623–634, 2006.

C. Chen and R. A. Beckman. Maximizing return on socioeconomic investment in Phase II proof-of-concept trials. *Clinical Cancer Research*, 20(7):1730–1734, 2014.

C. Chen, R. A. Beckman, and L. Z. Sun. Maximizing return on investment in Phase II proof-of-concept trials. In *Optimization of Pharmaceutical R&D Programs and Portfolios*, pages 141–154. Springer, 2015.

M. Colvin and C. T. Maravelias. A stochastic programming approach for clinical trial planning in new drug development. *Computers & Chemical Engineering*, 32(11):2626–2642, 2008.

M. Colvin and C. T. Maravelias. Scheduling of testing tasks and resource planning in new product development using stochastic programming. *Computers & Chemical Engineering*, 33(5):964–976, 2009.

L. Cui, J. Hung, and S. Wang. Modification of sample size in group sequential clinical trials. *Biometrics*, 55:853–857, 1999.

R. Curnow and C. Dunnett. The numerical evaluation of certain multivariate normal integrals. *The Annals of Mathematical Statistics*, pages 571–579, 1962.

C. De Boor. *A Practical Guide to Splines*, volume 27. Springer-Verlag, 1978.

D. L. DeMets and J. H. Ware. Group sequential methods for clinical trials with a one-sided hypothesis. *Biometrika*, 67 (3):651–660, 1980.

D. L. DeMets and J. H. Ware. Asymmetric group sequential boundaries for monitoring clinical trials. *Biometrika*, 69 (3):661–663, 1982.

J. D. Eales and C. Jennison. An improved method for deriving optimal one-sided group sequential tests. *Biometrika*, 79(1):13–24, 1992.

EAST-6. Software for the design and analysis of flexible clinical trials, 2019. URL `https://www.cytel.com/software/east`.

EMA. Reflection paper on methodological issues in confirmatory clinical trials planned with an adaptive design. 2007. URL `www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003616.pdf`.

K. Fairbanks and R. Madsen. P values for tests using a repeated significance test design. *Biometrika*, 69(1):69–74, 1982.

K. Fairbanks, R. Madsen, and R. Dykstra. A confidence interval for an exponential parameter from a hybrid life test. *Journal of the American Statistical Association*, 77(377):137–140, 1982.

FDA. Guidance document on adaptive designs for medical device clinical studies. Available at `https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-designs-medical-device-clinical-studies` (29/11/2019), 2017.

R. Fisher. *Statistical Methods for Research Workers*. Oliver and Boyd, 1925.

G. Gatica, L. Papageorgiou, and N. Shah. Capacity planning under uncertainty for the pharmaceutical industry. *Chemical Engineering Research and Design*, 81(6):665–678, 2003.

A. Genz, F. Bretz, T. Miwa, X. Mi, F. Leisch, F. Scheipl, and T. Hothorn. mvtnorm: Multivariate normal and t distributions. *R package version 0.9-2, URL http://CRAN. R-project. org/package= mvtnorm*, 2008.

J. Gittins and H. Pezeshk. How large should a clinical trial be? *Journal of the Royal Statistical Society: Series D (The Statistician)*, 49(2):177–187, 2000.

A. P. Grieve and M. Krams. ASTIN: a Bayesian adaptive dose–response trial in acute stroke. *Clinical Trials*, 2(4): 340–351, 2005.

L. V. Hampson and C. Jennison. Group sequential tests for delayed responses (with discussion). *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 75(1):3–54, 2013.

L. V. Hampson and C. Jennison. Optimizing the data combination rule for seamless Phase II/III clinical trials. *Statistics in Medicine*, 34(1):39–58, 2015.

J. E. Hewett and J. D. Spurrier. A survey of two stage tests of hypotheses: Theory and application. *Communications in Statistics-Theory and Methods*, 12(20):2307–2425, 1983.

A. Hirakawa, J. Asano, H. Sato, and S. Teramukai. Master protocol trials in oncology: Review and new trial designs. *Contemporary Clinical Trials Communications*, 12:1–8, 2018.

ICH. Statistics Principles for Clinical Trials E9. 1998. Regulatory Document.

W. F. Jacob and Y. H. Kwak. In search of innovative techniques to evaluate pharmaceutical R&D projects. *Technovation*, 23(4):291–296, 2003.

N. D. James, M. R. Sydes, N. W. Clarke, M. D. Mason, D. P. Dearnaley, J. Anderson, R. J. Popert, K. Sanders, R. C. Morgan, J. Stansfeld, et al. Systemic therapy for advancing or metastatic prostate cancer (STAMPEDE): a multi-arm, multistage randomized controlled trial. *BJU International*, 103(4):464–469, 2009.

C. Jennison. Discussion on Bayesian analysis of mixtures with an unknown number of components. *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 59(4):731–792, 1997.

C. Jennison and L. Hampson. Optimizing the data combination rule for seamless Phase II/III clinical trials. *Statistics in Medicine*, 34(1):39–58, 2015.

C. Jennison and B. W. Turnbull. *Group Sequential Methods with Applications to Clinical Trials*. CRC Press, 2000.

C. Jennison and B. W. Turnbull. Adaptive and nonadaptive group sequential tests. *Biometrika*, 93(1):1–21, 2006.

C. Jennison and B. W. Turnbull. Adaptive seamless designs: selection and prospective testing of hypotheses. *Journal of Biopharmaceutical Statistics*, 17(6):1135–1161, 2007.

K. Jiang. Optimal sample sizes and go/no-go decisions for Phase II/III development programs based on probability of success. *Statistics in Biopharmaceutical Research*, 3(3):463–475, 2011.

C. Kelly and J. Rice. Monotone smoothing with application to dose-response curves and the assessment of synergism. *Biometrics*, pages 1071–1085, 1990.

K. Kim and D. L. DeMets. Confidence intervals following group sequential tests in clinical trials. *Biometrics*, pages 857–864, 1987.

A. B. Kimball, M. M. Okun, D. A. Williams, A. B. Gottlieb, K. A. Papp, C. C. Zouboulis, A. W. Armstrong, F. Kerdel, M. H. Gold, S. B. Forman, et al. Two Phase 3 trials of adalimumab for hidradenitis suppurativa. *New England Journal of Medicine*, 375(5):422–434, 2016.

F. König. Confirmatory testing for a beneficial treatment effect in dose-response studies using MCP-Mod and an adaptive interim analysis. *Isaac Newton Institute*, 2015.

F. Lagarde, C. Beausoleil, S. M. Belcher, L. P. Belzunces, C. Emond, M. Guerbet, and C. Rousselle. Non-monotonic dose-response relationships and endocrine disruptors: a qualitative method of assessment. *Environmental Health*, 14 (1):13, 2015.

G. Lan and D. L. DeMets. Discrete sequential boundaries for clinical trials. *Biometrika*, 70(3):659–663, 1983.

W. G. Lechmacher W. Adaptive sample size calculations in group sequential trials. *Biometrics*, 55:1286–1290, 1999.

G. Lorden. 2-SPRT's and the modified Kiefer-Weiss problem of minimizing an expected sample size. *The Annals of Statistics*, pages 281–291, 1976.

D. Magirr, T. Jaki, and J. Whitehead. A generalized Dunnett test for multi-arm multi-stage clinical studies with treatment selection. *Biometrika*, 99(2):494–501, 2012.

D. Magirr, N. Stallard, and T. Jaki. Flexible sequential designs for multi-arm clinical trials. *Statistics in Medicine*, 33 (19):3269–3279, 2014.

O. Marchenko, J. Miller, T. Parke, I. Perevozskaya, J. Qian, and Y. Wang. Improving oncology clinical programs by use of innovative designs and comparing them via simulations. *Therapeutic Innovation & Regulatory Science*, 2013.

R. Marcus, P. Eric, and K. R. Gabriel. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika*, 63(3):655–660, 1976.

N. Metropolis and S. Ulam. The monte carlo method. *Journal of the American statistical association*, 44(247):335–341, 1949.

P. Müller, D. A. Berry, A. P. Grieve, and M. Krams. A Bayesian decision-theoretic dose-finding trial. *Decision Analysis*, 3(4):197–207, 2006.

H.-H. Müller and H. Schäfer. Adaptive group sequential designs for clinical trials: Combining the advantages of adaptive and of classical group sequential approaches. *Biometrics*, 57(3):886–891, 2001.

R. M. Neal. Slice sampling. *Annals of Statistics*, pages 705–741, 2003.

P. C. O'Brien and T. R. Fleming. A multiple testing procedure for clinical trials. *Biometrics*, pages 549–556, 1979.

U. D. of Health. Adaptive design clinical trials for drugs and biologics. *Guidance For Industry*, 2018.

A. O'Hagan, J. W. Stevens, and M. J. Campbell. Assurance in clinical trial design. *Pharmaceutical Statistics*, 4(3): 187–201, 2005.

S. Pampallona and A. A. Tsiatis. Group sequential designs for one-sided and two-sided hypothesis testing with provision for early stopping in favor of the null hypothesis. *Journal of Statistical Planning and Inference*, 42(1-2):19–35, 1994.

T. Parke, O. Marchenko, V. Anisimov, A. Ivanova, C. Jennison, I. Perevozskaya, and G. Song. Comparing oncology clinical programs by use of innovative designs and expected net present value optimization: Which adaptive approach leads to the best result? *Journal of Biopharmaceutical Statistics*, 27(3):457–476, 2017.

N. Patel, J. Bolognese, C. Chuang-Stein, D. Hewitt, A. Gammaitoni, and J. Pinheiro. Designing Phase 2 trials based on program-level considerations: a case study for neuropathic pain. *Drug Information Journal*, 46(4):439–454, 2012.

N. R. Patel and S. Ankolekar. A Bayesian approach for incorporating economic factors in sample size design for clinical trials of individual drugs and portfolios of drugs. *Statistics in Medicine*, 26(27):4976–4988, 2007.

N. R. Patel, S. Ankolekar, Z. Antonijevic, and N. Rajicic. A mathematical model for maximizing the value of Phase 3 drug development portfolios incorporating budget constraints and risk. *Statistics in Medicine*, 32(10):1763–1777, 2013.

T. Pham-Gia. On Bayesian analysis, Bayesian decision theory and the sample size problem. *Journal of the Royal Statistical Society: Series D (The Statistician)*, 46(2):139–144, 1997.

J. Pinheiro, B. Bornkamp, E. Glimm, and F. Bretz. Model-based dose finding under model uncertainty using general parametric models. *Statistics in Medicine*, 33(10):1646–1661, 2014.

S. J. Pocock. Group sequential methods in the design and analysis of clinical trials. *Biometrika*, 64(2):191–199, 1977.

M. Pollak and D. Siegmund. A diffusion process and its applications to detecting a change in the drift of Brownian motion. *Biometrika*, 72(2):267–280, 1985.

M. A. Proschan and S. A. Hunsberger. Designed extension of studies based on conditional power. *Biometrics*, pages 1315–1324, 1995.

A. E. Raftery, D. Madigan, and J. A. Hoeting. Bayesian model averaging for linear regression models. *Journal of the American Statistical Association*, 92(437):179–191, 1997.

S. Richardson and P. J. Green. On Bayesian analysis of mixtures with an unknown number of components (with discussion). *Journal of the Royal Statistical Society: Series B (Statistical Methodology)*, 59(4):731–792, 1997.

M. J. Rogers, A. Gupta, and C. D. Maranas. Real options based analysis of optimal pharmaceutical research and development portfolios. *Industrial & Engineering Chemistry Research*, 41(25):6607–6620, 2002.

H. Schmidli, F. Bretz, A. Racine, and W. Maurer. Confirmatory seamless Phase II/III clincial trials with hypothesis selection at interim: Applications and practical considerations. *Biometrics*, 48(4):635–643, 2005.

S. S. Senn. *Statistical Issues in Drug Development*. John Wiley & Sons, 2008.

D. Siegmund. Estimation following sequential tests. *Biometrika*, 65(2):341–349, 1978.

R. Simes. An improved bonferroni procedure for multiple tests of significance. *Biometrika*, 73(3):751–4, 1986.

E. L. Simpson, T. Bieber, E. Guttman-Yassky, L. A. Beck, A. Blauvelt, M. J. Cork, J. I. Silverberg, M. Deleuran, Y. Kataoka, J.-P. Lacour, et al. Two Phase 3 trials of dupilumab versus placebo in atopic dermatitis. *New England Journal of Medicine*, 375(24):2335–2348, 2016.

S. Solak, J.-P. B. Clarke, E. L. Johnson, and E. R. Barnes. Optimization of R&D project portfolios under endogenous uncertainty. *European Journal of Operational Research*, 207(1):420–433, 2010.

K. Solo, M. Paich, and L. SimNexus. A modern simulation approach for pharmaceutical portfolio management. In *International Conference on Health Sciences Simulation (ICHSS'04), San Diego, California, USA*, 2004.

N. Stallard. Sample size determination for Phase II clinical trials based on Bayesian decision theory. *Biometrics*, pages 279–294, 1998.

J. Temple. *Adaptive Designs for Dose-Finding Trials*. PhD thesis, University of Bath, 2012.

N. Thomas. Hypothesis testing and Bayesian estimation using a sigmoid Emax model applied to sparse dose-response designs. *Journal of Biopharmaceutical Statistics*, 16(5):657–677, 2006.

N. Thomas, K. Sweeney, and V. Somayaji. Meta-analysis of clinical dose–response in a large drug development portfolio. *Statistics in Biopharmaceutical Research*, 6(4):302–317, 2014.

V. A. Varma, J. F. Pekny, G. E. Blau, and G. V. Reklaitis. A framework for addressing stochastic and combinatorial aspects of scheduling and resource allocation in pharmaceutical R&D pipelines. *Computers & Chemical Engineering*, 32(4-5):1000–1015, 2008.

A. Wald. *Sequential Analysis*. Courier Corporation, 1947.

A. Wald and J. Wolfowitz. Optimum character of the sequential probability ratio test. *The Annals of Mathematical Statistics*, pages 326–339, 1948.

J. M. Wason and T. Jaki. Optimal design of multi-arm multi-stage trials. *Statistics in Medicine*, 31(30):4269–4279, 2012.

J. Whitehead. On the bias of maximum likelihood estimation following a sequential test. *Biometrika*, 73(3):573–581, 1986.

B. E. Wittes J. The role of internal pilot studies in increasing the efficiency of clinical trials. *Statistics in Medicine*, 9: 65–72, 1990.

M. Worm, S. Zielen, T. Higenbottam, O. Pfaar, R. Mosges, W. Aberer, M. Kramer, M. Skinner, and B. Lees. Selection of the optimal dose for an ultra-short course subcutaneous immunotherapy (scit) for rhinoconjunctivitis for birch allergic patients. *Journal of Allergy and Clinical Immunology*, 139(2):AB150, 2017.