Optimal Decision Making in Clinical Trials

Nikolaos Tsikouras
Department of Mathematics
Lancaster University

Supervisors: Peter Jacko & Andrew Titman

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Nikolaos Tsikouras.
Department of Mathematics, Lancaster University

Abstract

It is known that the most important type of experiment in clinical trials is Randomised Clinical Trials (RCT). RCTs have been the gold standard for over 70 years and will probably continue to do so as they have a very important property; they maximise power. However, during the past few years, as well as due to the unexpected COVID–19 pandemic, clinicians have started to look for more effective ways of conducting RCTs. In the first part of this thesis we introduce some of the most common types of RCTs with their advantages and limitations. Next, we turn our attention to the main goal of this research project; guiding in the decision–making of pharmaceutical companies. This is usually done in one of three ways; (a) a combination of frequentist and Bayesian methods, (b) Machine Learning methods, and (c) Markov Decision Processes within the Bayesian framework. For all three we provide the most interesting methods in the literature, before giving our novel contribution to this field. We use a Markov Decision Process model to calculate the optimal decision of the combination of Phase II (binary endpoint) and Phase III (two–armed, randomised 1:1 allocation) designs. We simulate several examples to showcase how our method would perform in practice, and indicate the strengths and limitations of it. Finally, we address these limitations in the last part of the thesis where we also conclude with our future plans for this research project that will potentially lead to a Ph.D.

Contents

Chapter 1

Introduction

1.1 Stating the Problem and Motivation for the Thesis

Clinical trials are one of the most important types of experiment that need to be conducted in the field of clinical research. They are the only way for a treatment to be given a license and start to get used in practice. Usually they involve two groups of people, the treatment and the control group, and the aim is to identify if the new treatment is safe and effective, as well as other factors such as effective dosage.

There are normally 3 Phases for every clinical trial. Phase I is a small scale study which aims to examines the drug's safety and tolerability (Hampson et al., 2022). Succeeding in this stage leads to Phase II which is usually divided in Phase IIa and Phase IIb. In the first of the two, researchers seek evidence of effectiveness and in the second part, dose and dosing schedule is identified, which would eventually be used in Phase III of the trial (Hampson et al., 2022). If the results from Phase II look positive, a Phase III confirmatory trial is conducted to provide more evidence of the treatment effect on the overall survival of the patients (Hong and Shi, 2012).

However, the main problem is that despite the surge of knowledge and research about the molecular basis of diseases (Joseph A DiMasi, Reichert, et al., 2013) the probability of a drug transitioning to a New Drug Application after making it to Phase III is lower than 40% (Arrowsmith, 2011; Feijoo et al., 2020) and the failure rate of a Phase II trial is 75% (Harrison, 2016). In total, around 11% of experimental drugs progress from Phase I to receive final regulatory approval (Hay et al., 2014). The high failure rates in Phase I and Phase II trials are somewhat justified, as these are exploratory trials, as we mentioned. However, the low success rates of the confirmatory Phase III trials is quite high, which is not intuitive as theoretically if early trials show promising results, relatively few Phase III trials should fail (Pretorius, 2016). There are probably a multitude of reasons for why this issue exists. Unreliable models (Prinz, Schlange, and Asadullah, 2011), biased datasets from unreported clinical trials (Goldacre et al., 2018) and broader issues such as forced decisions due to time constraints (Arrowsmith, 2011) certainly lie at the core of this issue amongst other factors.

The above combined with the fact that the cost of developing a new drug is estimated between US$600 million to US$2.8 billion (Carroll, 2013; Joseph A DiMasi, Grabowski, and Hansen, 2016), makes evident that these high failure rates are not sustainable (Chuang-Stein et al., 2011). Thus, the goal of investors and pharmaceutical companies is to find effective ways to properly estimate the likelihood of approval and decide whether the risk of developing a new drug is more significant than the expected revenue in the long run. We note here that an additional time constraint is taken into consideration for these decisions as the drug patents usually last 20 years, so the aim is to have as much of the remaining time as possible, to

maximise revenue.

To tackle these issues one can approach the problem from quite different perspectives. For example providing clinical investigators ways of designing better studies and giving methodologies of interpreting trial results more informatively (D. M. Halperin et al., 2015). Additionally, a large part of the literature focuses on measuring the risk of failure after Phase IIb, since after this Phase a major investment is usually required so as to create large-scale pivotal Phase III studies are initiated (Hampson et al., 2022). From here, certain metrics can be used to inform decision makers (J. DiMasi et al., 2015). A key metric used for risk quantification is the probability of success (PoS), and many attempts have already been proposed to estimate it for different clinical trial settings. Examples include (Hampson et al., 2022; O'Hagan and Stevens, 2001; Wang et al., 2013).

1.2 Aim of the Thesis

The aim of this thesis is initially to provide the reader with an overview of the traditional clinical trials with some of their extensions that have recently started becoming popular, showcasing their strengths and weaknesses. In addition we aim to provide a review of the most interesting methods in the literature that can be used within clinical trials to provide information on the likelihood of a new drug approval. These include several methods, from which we shall briefly see three. A combination of frequentist and Bayesian approaches, some Machine Learning methods that are used to provide insights from data which help clinicians and investors make more informed choices. And finally, methods that use Markov Decision Processes within the Bayesian framework to find optimal decisions.

Furthermore, our contribution with this thesis is a novel model that uses a Markov Decision Process to optimally select designs for the combination of Phase II – Phase III trials. Later, we aim to extend this model to a more realistic one so that it can eventually be used in the context of lung cancer clinical trials which is the ultimate goal of our research. Finally, we aim to provide the reader with several further directions of this work which will be the starting point for a potential Ph.D.

1.3 Structure of the Thesis

The rest of this thesis is structured as follows; Chapter 2 is a literature review on the clinical trials methodology where we discuss the most common ways of conducting a clinical trial as well as giving the benefits, limitations, and challenges of each. Next, in Chapter 3 we provide a description and a review on the three different approaches pharmaceutical companies use to guide their decisions; estimating the probability of success via a combination of frequentist and Bayesian methods, using Machine Learning methods, and using Markov Decision Processes. In Chapter 4 we provide our contribution to this field by giving a novel Markov Decision Process model which returns the optimal policy on the combination of Phase II – Phase III designs. We test our method in several scenarios and present how it would work in practice as

well as provide a simulation to showcase some of the strengths and limitations of it. Finally, in Chapter 5 we conclude this thesis by briefly summarising the main concepts, discuss how we can overcome the limitations of our method and provide short and long term plans for the future.

Chapter 2

Different Clinical Trial Designs

2.1 Progression of Clinical Trials Over the Years

In this Chapter we give a summary of the most common clinical trials starting from the traditional randomised clinical trials and reaching the more modern ones. The aim of this Chapter is for the reader to understand that different clinical trials exist each with its advantages and disadvantages and it is up to the practitioners and the investors to choose the optimal one.

2.1.1 Traditional Clinical Trials

Randomised Clinical Trials (RCTs) have been the gold standard in demonstrating the efficacy of a drug since 1948 (Redman and Allegra, 2015), and this is due to the fact that they detect significant treatment differences with high probability, or to put it more simply they maximise power (Williamson, Jacko, Villar, et al., 2017). An RCT is an experiment in which a new proposed treatment is compared against a placebo or an existing benchmark which we refer to as control. RCTs have changed little in the last 70 years, and have been purposely been left simple and straightforward.

The traditional formulation of an RCT has the following methodology. Initially we have two arms, the treatment medication and control medication, and a fixed number of people are recruited and randomly assigned to one of the two arms keeping in mind the desired ratio (usually 1:1). Then, in consequent follow ups clinicians examine the patients (note that some may have stopped being part of the RCT for various reasons), and gather all information required, usually some key endpoints for example blood pressure, cholesterol levels etc. Finally, at the end of the trial, the collected data are analysed and inference is made.

However, the rate of drug development in various disease categories has accelerated recently (Bratton, Phillips, and Parmar, 2013). Despite this, the rate at which novel medicines are reaching patients has slowed (Food et al., 2004). This is mostly caused by the rising cost and the slowness of the drug development process, as well as by the fact that most novel therapies do not clearly outperform existing ones. The RCT has served as the foundation upon which advancements in clinical research have been tested over the past 70 years. There is little doubt that the use of this strategy has significantly improved the lives of people with different diseases. The RCT will continue to be the gold standard when it comes to clinical research and will be necessary in many situations, but the pace of development in the scientific and technology fields is changing the regulatory environment and showcasing a major disadvantage (Cave, Kurz, and Arlett, 2019).

Due to their nature they can only ask a single question each time, and even though this

would be a large step in understanding and curing diseases in the past, we can say that now it is only is a small step in that direction (D. A. Berry, 2015). This holds because in the past we had a small number of therapies to investigate and diseases were considered "homogeneous". Since the first complete human genome was published in 2003, biomedical technology has advanced rapidly, and diseases such as cancer can be cured using precision oncology by widely available, reasonably priced next–generation genomic sequencing (Redman and Allegra, 2015). This means that the disease is subdivided into smaller groups and soon every cancer patient will have an "ultra-orphan" form. It is clear that conventional 2–arm parallel group RCTs have emerged as one of the rate limiting variables of the drug development process, and more flexible trial designs are required (Meyer et al., 2020) that take less time to complete and answer more than one question.

2.1.2 Adaptive Clinical Trials

As already mentioned, the major advantage of traditional RCTs is that they maximise power. Although this can be beneficial for future patients, as they are more likely to pick up on an effect, they lack the flexibility to include other factors, an example would be to maximise the percentage of patients enrolled in the trial who will be getting the superior treatment. In RCTs, it does not matter if there are indications that any of the two treatments is inferior, half of the patients are going to receive it. This is clearly not an optimal strategy to follow, especially when we are dealing with a rare disease in which a relatively large proportion of the population might be included in the trial (Williamson, Jacko, Villar, et al., 2017). Another thing to note is that in the case of a rare disease, there will be relatively less active patients outside the trial to benefit from the high power RCTs offer.

Reasons such as this motivated the development of adaptive clinical trials, as the flexibility they provide helps account for more factors than just maximising the power of the trial. To put it more formally, "an adaptive design is a design that allows changes to the trial and/or statistical procedures of the trial after its initiation without undermining its validity and integrity" (Pharmaceutical Industries and Associations, 2020).

Adaptive trials started to become more popular both theoretically and in practice in the late 1990s but became widely discussed in the early 2000s and they have started to be used increasingly in recent years (Demant et al., 2014; Freidlin and Simon, 2005). Adaptive study designs allow changes in a design component; examples include sample size, randomisation ratio, treatment arms, stoppage at specific points of a Phase (also known as interim analysis) based on accumulated data from study participants while fully controlling Type I error. The general consensus in the scientific community is that they should be used in situations where a traditional RCT is difficult or unethical to be performed, such as in the case of a rare disease (Agency, 2007), or when the goal is to reduce time and cost of drug development while maintaining high power (Mahlich, Bartol, and Dheban, 2021). Below, we see some of the most common ways to make trials adaptive. We note that we deliberately leave response adaptive randomisation for a later subsection as it fits in a different type of trial too.

2.1.2.1 Early Stopping for Futility

This type of adaptation is particularly useful for investors as it allows for a trial to be stopped at an interim analysis point using some statistical measure which estimates the probability of success of the trial. This way, if a trial's results do not look particularly optimistic, patients and funds can be allocated to different trials which perhaps would lead to better results. It can also be argued that this type of adaptation is also ethical if the early data are substantially negative as less patients will be given inferior treatment. A possible issue with this type of adaptation is the drop of statistical power of the trial. To help counter this, trial designers could set more conservative stopping boundaries. It is up to them to balance this trade-off between ability to detect futility early and the loss of power.

We note that regulators like the EMA/FDA do not generally allow futility stopping rules to be taken into account when computing the Type I error. The reason behind this is that they do not believe the futility stopping rule will be necessarily adhered to. Instead, designs usually include a "non–binding futility rule", meaning it is a guideline that may or may not be followed, and is assumed to not hold when calculating the Type I error, but can be considered in the power and overall optimisation of the design (GUIDANCE, 2018).

Early stopping for futility has been discussed since the 1980s (M. Halperin et al., 1982), and there is an increasing number of research and number of trials (Jitlal et al., 2012) that incorporate this kind of adaptation.

2.1.2.2 Early Stopping for Efficacy

The second most common form of adaptation is stopping early for efficacy and has started to be increasingly used (Bassler et al., 2008). Contrary to stopping for futility, in this form of adaptation, the trial would stop at an interim analysis point if there is a substantial amount of information/data that are overwhelmingly positive. Again, this would lead to more patients and resources being allocated to different trials, as well as potentially receiving a license considerably earlier, leading to an effective treatment becoming available earlier.

It should be noted that trials that were terminated early due to efficacy should be carefully viewed, since statistical stopping procedures are susceptible to terminating trials at random highs that overstate the expected impact of treatment. Other things to consider in this type of adaptation are the amount of interim analysis points, the timing of them, and the fact that there should be at least a minimum amount of information collected so as to not inflate the Type I error. Another common issue is that this type of adaptation only considers information available at the time of interim analysis, which frequently includes patients who have been recruited for the study but have not yet shown a response to treatment, thus accurate ways of dealing with censored data are required.

2.1.2.3 Sample Size Adjustment

Another type of adaptation is the sample size adjustment and it can either be blinded or unblinded. The idea behind this type of adaptation is that there is a chance that small-scale studies will not show statistically significant proof of the efficacy (Li et al., 2002). On the

contrary, using excessively large sample sizes is a waste of resources. For these reasons, at the specified interim points the current accumulated data are analysed and, if required, the additional sample size is measured, with the main goal to preserve the prespecified power of the trial.

Blinded adjustments are usually used to deal with some of the incorrect assumptions practitioners make when designing a trial. They are mainly done in order to not increase the Type I error. On the other hand, unblinded adjustments are used when the results for the treatment effect are worse that expected but still look optimistic. It is usually an investment decision point, where investors can decide whether to increase the sample size or stop the trial.

2.1.3 Master Protocol Clinical Trial Designs

The need to test multiple new targeted agents both alone and in combination with other targeted treatments also gave birth to a new therapeutic platform referred to as master protocol. This new therapeutic platform is capable of assessing experimental therapies in multiple subgroups of a study population (Meyer et al., 2020) as well as evaluating various experimental drugs or experimental therapy approaches in relatively limited patient subpopulations quickly and efficiently all within the same overall clinical trial structure (Redman and Allegra, 2015). Furthermore, because numerous subgroups operate simultaneously, there is a higher likelihood that patients will meet the requirements for at least one of the subgroups. Sharing of patients across the entire research may be possible if inclusion and exclusion criteria are identical (Meyer et al., 2020). There exist three different types of clinical trial designs under master protocol: basket trials (for researching a new therapy in a number diseases), umbrella trials (for researching a number of new therapies in one disease), and platform trials (for researching multiple simultaneous treatments for one disease), and we provide an overview of each one of those below.

2.1.3.1 Basket Clinical Trials

In recent years, the development of biomarkers and personalised medicine has led to drastic changes in the treatment of patients. We are possibly being led to a future where every disease is "rare", meaning a disease specialised to a very specific group of patients (Saville and S. M. Berry, 2016). This means that large–scale RCTs, which were designed to evaluate new treatments for groups of homogeneous patients, will become impractical. Therefore, this has led clinicians to develop basket clinical trials, which analyse the effect of one specific treatment to several groups of patients, by establishing eligibility based on the presence of a certain genetic biomarker or a genetic characteristic that is connected to the treatment's therapeutic target, (Meyer et al., 2020; Tao, Schram, and Hyman, 2018).

For example, in oncology where basket trials have begun to be increasingly used (D. A. Berry, 2016), basket trials go against the tradition of organ–specific definition of cancer, and instead of testing a treatment for a specific cancer type, the main organising feature of a basket trial is the molecular alteration (Tao, Schram, and Hyman, 2018). The procedure is as follows. After determining the organ site, molecular aberrations of the tumour are evaluated.

Then, medications are licensed for cancer in a specific organ that contains a certain molecular characteristic rather than the opposite. Although basket trials are currently more popular in Phase II, they are being investigated for Phase III (D. A. Berry, 2016).

Due to their nature basket trials offer quick identification of several potential treatment indications. Additionally, in arms where patients are exhibiting low responses, immediate termination is possible. Another significant benefit is that it is possible to research a variety of rare diseases when there are few patients and gather more safety data than with individual trials. Basket clinical trials can also be used in settings where several diseases and disease subtypes may react to the same or related treatments, even across different fields. An immunotherapy, for instance, could be successful in treating cancer, arthritis, and sepsis (D. A. Berry, 2016). Finally, basket trials are quicker to complete than individual studies for each indication, which can speed up development, reduce costs, and assist the quick approval of new treatments.

Finally, we end this introduction to basket trials by presenting some of their limitations. Perhaps the most basic one is that basket trials may have arms with small sample sizes that are challenging to analyse. To accurately choose the trial arms that should be continued or discontinued and prevent a selection bias based on chance findings in a small number of patients, high treatment efficacy is a requirement. Additionally, finding the few patients that match the disease profile the medication is targeting can be challenging and would probably require having many people tested. Finally, there seems to be some bureaucratic issues as well, as the complexity of basket trials can lead to extensive protocols which can cause problems to ethics committees and investigators (Pharmaceutical Industries and Associations, 2020). This means that each trial site must have enough principal investigators and resources to cover each indication in a basket study, which is often costly and difficult. Another tailored intervention clinical trial is the umbrella trial which we present next and as we shall see has a key difference to basket trials.

2.1.3.2 Umbrella Trials

The umbrella trial is another variation on a master protocol in which a number of targeted medicines are assessed for a single disease that has been divided into several subgroups based on various genetic or other prognostic risk factors (Meyer et al., 2020). When a disease has several genetic mutations or when various effective medications and therapy alternatives are being tested for the same condition, umbrella trial designs can be helpful. Several different treatment arms may be included in a single protocol of an umbrella trial, or alternatively, a general screening protocol may be combined with various unique protocols for each distinct treatment option (Woodcock and LaVange, 2017).

Umbrella trials are also increasingly used in cancer research (Park, Hsu, et al., 2020), but compared to basket trials they are focused on patients with a single disease histology, rather than a specific genomic alteration (Simon, 2017). The procedure of an umbrella clinical trial is as follows. Assume that possible treatments are being looked for a single type of cancer. Then that type of cancer is separated into different subgroups and each of the treatment arms' eligibility is biomarker-guided, meaning that it is determined by its mechanism of action of

each treatment.

In the biomarker era of modern biology, using umbrella trials, which by design group many biomarkers under a single trial, makes avoiding the screening of patients more than once easier, lowers the screening failure rate, and raises the possibility that a patient will be qualified to take part in a study. In addition, a huge benefit is the allowance for direct comparison of various treatments for diseases. Umbrella trials' diverse strategy is bound to accelerate development, reduce costs, and assist in the rapid approval of novel treatments. Overall, umbrella trials are considered to be quite operationally efficient (Lu et al., 2021).

Umbrella trials come with certain drawbacks; first there are statistical issues with adding additional treatment arms after a trial has begun due to the possibility for bias introduction when compared to the initial trial's treatments and control. Treatment assignment and classification is frequently based on biomarkers; therefore, numerous biomarkers must be screened centrally because local genotyping can produce less reliable results (Pharmaceutical Industries and Associations, 2020). We also note here that each novel diagnostic biomarker has to go through a regulatory approval process and needs to be confirmed, which might cause delays. Finally, as new treatments become available, the standard of care for a disease can change over the course of extensive trials, possibly necessitating changes in the control arm's therapy, which could have an impact on statistical inferences (Pharmaceutical Industries and Associations, 2020). Next, we investigate a final design under the master protocol, platform clinical trials.

2.1.3.3 Platform Clinical Trials

As mentioned above, there have been many advances in personalised medicine in the past few years, leading to progressively more complex treatment regimens (Saville and S. M. Berry, 2016). Additionally, it is increasingly more typical for several novel treatments to be made available for testing in clinical trials at the same time due to the accelerated pace of drug development. An example is Tuberculosis, for which in 2013 there were at least ten new or repurposed medications in the clinical pipeline for treating it (Lienhardt et al., 2012; Ma et al., 2010). One of the issues here is that if we had to evaluate each new treatment against a control in independent two–arm trials, then this would require a large amount of resources. Additionally, the most efficient and simplest new regimens might not be available to patients as soon as possible, which should be the main goal. Therefore, there is an urgent need for creative trial designs that can effectively evaluate several potential treatments at the same time.

This led researchers to yet another clinical trial design, platform trials. Platform trials were developed to answer the question "which treatment or combination of treatments is ideal for each kind of patient?" (Saville and S. M. Berry, 2016). To put it simply, platform trials evaluate multiple treatments, across several groups of patients, and are particularly useful for testing combinations of treatments, as well as for direct comparisons between rival treatments, both of which are frequently disregarded in premarket contexts (Saville and S. M. Berry, 2016). An added benefit of platform trials that reduces costs greatly and boosts statistical efficiency is sharing resources in platform trials possibly among several sponsors (Saville and S. M. Berry, 2016).

There exist two common subgroups of platform clinical trials: Multi–Arm Multi–Stage (MAMS) and Response Adaptive Randomisation (RAR) trials (Lin and Bunn, 2017). MAMS designs are used to decide whether experimental treatment arms should be dropped using predetermined stopping boundaries and treatment selection guidelines (Lin and Bunn, 2017). They were first proposed in 2001 (Bookman et al., 2009) as an adaptive clinical trial design for ovarian cancer with an interim analysis for futility after every stage, and were mostly developed for time–to–event endpoints (Phillips et al., 2012). In MAMS designs each of the several experimental arms is compared pairwise with the control (Royston et al., 2011), just as a typical platform trial. Due to their efficiency, they have seen an increase in use, especially in late Phase trial settings (Noor et al., 2022). However, we should note here that in a standard MAMS trial there should not be any new treatment arms added after the start of the trial, but in practice it seems that the influence of platform clinical trials has relaxed this. There exist MAMS trials in which all the initial experimental arms have been changed (e.g. the STAMPEDE trial) (Millen and Yap, 2020).

On the other hand, in a Response Adaptive Randomisation (RAR) design, the randomisation ratio, i.e. percentage of ratio allocated to each treatment, is adjusted giving preference to a treatment having a higher probability of success thus giving more patients access to the (current) best–performing treatment (Lin and Bunn, 2017). The use of RAR designs is debatable, and it is generally accepted that because of the loss of power, they should not be used. However, there are circumstances in which RAR designs make trials more ethical (e.g. rare diseases), since overall more patients will be allocated to the superior treatment, although this is still debated in the literature. Additionally, since by design there is a greater likelihood that a patient will be paired with a better performing arm, this makes them more appealing to clinicians and prospective patients.

Response adaptive trials have a long history in clinical trials methodology (Rosenberger, 1996), but very few have been implemented in practice. The reason behind that is perhaps due to a single clinical trial known as the ExtraCorporeal Membrane Oxygenation (ECMO) trial (Bartlett et al., 1985), which was disappointing.

The disadvantage for both MAMS and RAR designs is the fact that delays in recruitment as well as delays in responses following enrollment have been shown to have a negative influence on both types, especially on the expected sample size (Lin and Bunn, 2017).

In general, platform trials can have a fixed number of treatments or an adaptive number of treatments, where treatments can be discarded or added as the trial progresses. Additionally, traditional platform trials involve different therapies from different pharmaceutical companies. Having an adaptive number of treatments is what is referred to as an open or perpetual platform trial since it is perpetual as long as new experimental treatments can be enrolled in it. Compared to conventional approaches that focus on one treatment at a time, such platform trials can uncover successful treatments considerably more quickly and with less funding (Saville and S. M. Berry, 2016). Additionally, they do not need a brand-new trial infrastructure for each treatment that is being studied.

However, despite all the benefits, for these trials to be effective, a sizable number of patients must be enrolled. This can be challenging, especially for rare diseases. Second, because they

require the use of numerous medications and/or technologies, platform clinical studies can be costly. Third, platform clinical trials can take a long time, since they frequently include numerous treatment regimens and/or treatment arms. Finally, because they frequently involve a number of stakeholders, platform clinical trials can be complicated leading to bureaucratic issues.

Over the last few years, registered platform clinical trials have increased (Park, Hsu, et al., 2020). Numerous diseases, including breast cancer (Esserman and Woodcock, 2011), lung cancer (Zhou et al., 2008), pandemic influenza (Saville and S. M. Berry, 2016), Ebola (Saville and S. M. Berry, 2016), have undergone successful platform trials or are currently undergoing planning. Both Phase II and Phase III stages are included in these. Furthermore, the COVID–19 pandemic appears to have given this type of trial a surge of use, as they appear to be highly suited for producing evidence quickly (Vanderbeek et al., 2022). However, in a recently published study (Saville and S. M. Berry, 2016), it was argued that despite the obvious advantages of platform trials, there is still more room for them to be used in actual practice, and the authors' reasoning behind it was that many researchers are unaware of these advantages.

2.2 Biggest Challenges of the Industry

The business model of the pharmaceutical sector is undergoing unheard of challenges (Paul et al., 2010). Even knowledgeable individuals and market gurus have anticipated its forthcoming downfall (Lindgardt, Reeves, and Wallenstein, 2008). Ignoring the public's concerns about the transparency and integrity of the sector, which, of course, has increased regulatory attention as a result of the reputation of the sector (Angell, 2005), pharmaceutical companies also face profitability issues. Simply put, the pharmaceutical industry of today cannot sustain enough innovation to make up for the income losses caused by the patent expirations of successful drugs without a significant boost in R&D productivity.

A significant obstacle in achieving R&D productivity are the flaws of human thinking, as there seems to be a strong bias to engage in "progression–seeking" behaviour (Ringel et al., 2013). It is believed that many low-viability compounds are intentionally moved to later stages of development. Making the correct decision regarding which treatments to progress to late-stage clinical trials is crucial in increasing productivity. To emphasise this more, researchers from Pfizer published a compelling study demonstrating that, based on the facts at hand, it was possible to anticipate that two-thirds of the company's Phase I assets would fail (Morgan et al., 2011).

We believe that to help change the above, the teams responsible for the development of a new drug should behave more rationally and base their decisions on data and precise methodologies rather than beliefs. More simply put, teams should be truth–seeking rather than progression–seeking, which in turn would take the whole field a step forward. This leads us to the next Chapter in which we shall see several methods already used in practice and we shall give our own model to help tackle this problem.

Chapter 3

Existing Work on Decision Making in Clinical Trials

The focus of this Chapter is to give the reader a broad view of the literature surrounding decision–making in clinical trials. We aim to show the reader why research in this field is important and provide our understanding of what is coming next. The rest of this Chapter is organised as follows; first estimating the probability of success approach is considered, where the idea is to combine frequentist methods together with incorporating prior knowledge to express evidence of the treatment effect to inform a posterior probability for a drug approval. The next approach we consider is the Machine Learning approach, where meaningful data is gathered with the goal of combining them with certain algorithms to give insights on the probability of approval of the considered treatment. Finally, the Markov Decision Process approach is considered, which lately seems to be on the rise. This approach fits naturally in the decision making framework as Markov Decision Processes can be used to find optimal decisions in a dynamic system.

3.1 Estimating the Probability of Success

It has been made evident that investing in clinical trials is associated with high risk. As a result, before making a financial commitment to a clinical trial, sponsors usually want to determine the likelihood that the study will be successful. By having an accurate estimate of the Probability of Success (PoS), one can calculate the expected Net Present Value (eNPV), defined as eNPV = PoS $\times$ NPV(Rewards) - NPV(Costs) (Hampson et al., 2022). The eNPV is a metric that gives an estimate of the risk and value of the drug development and allows investors to make informed decisions.

One could naively think that by ensuring high statistical power (usually 80% or above), we could reliably solve this problem; however, this is not the case. It turns out that the success rate of clinical trials, when the novel treatment is actually better than the control, is substantially lower than the pre–specified power, therefore traditional statistical power fails to solve this problem (Wang et al., 2013). The reason for that is because power is the likelihood of success (reaching statistical significance) assuming a specified effect size, but how can one know the true effect size? In practice, the assumed effect size may not be supported by existing data or accurately reflect the effect of treatment and is frequently dependent on regulatory, payer and marketing requirements or needs (Wang et al., 2013).

For these reasons, there are several alternative ways to define PoS in the literature (Hampson et al., 2022) and it is up to the authors to decide which one they use. We present two of the most common definitions expected power and prior–adjusted power, we note however

that this is by no means an exhaustive list (Ciarleglio et al., 2015; Dallow and Fina, 2011). The interested reader can find a comprehensive list at (Kunzmann et al., 2021).

3.1.1 Using Expected Power

The first definition we consider is the Expected Power (EP) or assurance which was introduced by (O'Hagan and Stevens, 2001), and is a combination of frequentist and Bayesian concepts (Wang et al., 2013). This definition corresponds to the unconditional probability of rejecting the null hypothesis (i.e. yielding a positive trial outcome) regardless of the value of the relevant parameter.

The idea behind this definition is the following: when designing a clinical trial, the sample size is frequently set to reach the desired power conditional on a specified treatment effect. In reality there is a great deal of uncertainty around what the actual underlying treatment effect may be and traditional power is unable to incorporate this. This inability led to the idea of taking the expectation of conventional power with respect to a prior for the true underlying treatment effect. EP is an improvement over power in measuring the likelihood of success for the new trial, as it gives an overall predictive probability of a successful outcome by using current understanding of the treatment effect in the form of a prior distribution. Having said that, we view the true treatment effect θ as a realisation of a random variable and give the following definition for EP:

$$\text{EP} = \int_{-\infty}^{\infty} \mathbb{P}(\text{study success}|\theta)\mathbb{P}(\theta)d\theta, \tag{3.1}$$

where $\mathbb{P}(\text{study success}|\theta)$ in Equation 3.1 is the classical statistical power at θ and $\mathbb{P}(\theta)$ is the prior distribution of the treatment effect given the current knowledge of the drug. Therefore intuitively EP is a weighted average of the probability to reject the null hypothesis or the expectation of the power function with regard to a prior distribution for the actual underlying effect size. This definition of PoS suggests that rejection of the null hypothesis, regardless of its veracity, must be seen as a success.

Analytical evaluation is possible in limited scenarios (Spiegelhalter, Abrams, and Myles, 2004). In most situations both quantities in Equation 3.1 are going to be complex, thus the integral can be estimated using simulations (Spiegelhalter, Abrams, and Myles, 2004).

3.1.2 Using Prior Adjusted Power

A similar definition of PoS was given in (Spiegelhalter and Freedman, 1986) where the authors defined PoS by integrating the likelihood of having a successful trial (i.e. rejecting the null hypothesis) conditional on the truth that the treatment effect is relevant. This means that the treatment effect is at least greater than some minimal clinically relevant difference, $\theta > \theta_{MCID}$. This quantity, named Prior–Adjusted Power (PAP) mathematically is defined as:

$$\text{PAP} = \int_{\theta_{MCID}}^{\infty} \mathbb{P}(\text{study success}|\theta)\mathbb{P}(\theta)d\theta, \tag{3.2}$$

This is a tight definition of success, which indicates that a trial is considered a success if the null hypothesis is rejected and the treatment effect is at least clinically relevant. Again, analytical evaluation of Equation 3.2 might not be feasible, therefore numerical estimations are required (Rufibach, Burger, and Abt, 2016).

Depending on the viewpoint, a pharmaceutical company might just be interested in rejecting the null hypothesis to profit from a new drug, regardless of whether it truly exhibits a relevant effect. This view would be in line with the EP. Regulators and businesses may lean toward the combined probability of properly rejecting the null because they are concerned about the longer–term effects of potentially having to withdraw ineffective drugs; in that case, PAP is the correct tool. Thus, it is up to the researcher to define and reason what definition they are using.

3.1.3 Incorporating Multiple Sources of Information for Decision Making

Similarly to the previous introduction to probability of success, the authors in (Hampson et al., 2022) concentrated on estimating the probability of a trial succeeding prior to starting registration trials, which usually start at the conclusion of Phase II. Programme success was defined as regulatory approval with effects on key endpoints that are sufficient to give a newly approved drug access to the market.

The method proposed is a quantitative Bayesian method that takes into account internal clinical data from one or more Phase IIb studies, industry–wide success rates, expert opinion, and if necessary, external data for determining the PoS at the end of Phase II. Interestingly, since the end of 2020 Novartis has formally adopted the use of this methodology in estimating PoS prior to the start of pivotal studies which require the largest investment. This is not a surprising achievement as, to the best of our knowledge, this methodology, although may take more time and effort than simpler methods, it uses and incorporates much more of the available information and expert knowledge which justifies the extra effort.

The core of the proposed methodology is based on three different hurdles for a drug's success. In particular, there is the need to: (a) obtain regulatory approval; (b_1) meet statistical significance on the one or two efficacy endpoints required for approval in all Phase III trials (b_2) without observing a Safety Showstopper Event (SSE), which essentially is any adverse event that might force the termination of a clinical programme despite having encouraging data; and (c) observe treatment effect estimates that are higher than the minimal levels deemed necessary to gain access for all efficacy endpoints considered essential for market access, called Target Product Profile (TPP). The proposed model integrates information from a number of sources and using points (a)–(c) gives an estimation of the PoS via the following formula,

$$\begin{aligned}\text{PoS} = &\overbrace{\mathbb{P}(\text{Efficacy success on key endpoints})}^{(b_1)} \times \overbrace{\mathbb{P}(\text{No SSE in Phase III})}^{(b_2)} \\ &\times \underbrace{\mathbb{P}(\text{Approval and TPP} \mid \text{Efficacy on key endpoints and no SSE in Phase III})}_{(a,c)} \quad (3.3)\end{aligned}$$

The likelihood of a successful Phase III trial (points (b_1,b_2)) in which efficacy can be shown on the chosen key endpoints without observing an SSE uses a simplifying assumption that a programme can only fail due to being either not effective enough or not being safe. This allows the split we see on the first line in Equation 3.3. The first part (b_1) is calculated using a simulation approach with a Bayesian meta–analytic model which integrates the Phase IIb data while accounting for discrepancies between studies. To calculate the probability of observing no SSE in Phase II (point (b_2)) they use a logistic regression fitted to industry data. Finally, the "programme's conditional PoS" (points (a,c)) includes risks identified at the end of Phase IIb that have not yet been taken into consideration in the previous two points. For this reason, experts' opinions are considered by several surveys, and a generalised linear mixed model is used to connect the average opinion on the conditional PoS to the answers in the aforementioned surveys, to give the probability required. Combining all of the above gives an estimate of the PoS of a programme at the end of Phase II.

3.2 The Machine Learning Approach

Predicting the outcomes of clinical trials is a problem well–suited for Machine Learning (Lo, Siah, and Wong, 2018), an interdisciplinary area that focuses on solving pattern recognition issues and creating prediction models to make data–driven judgments. Most Machine Learning techniques produce estimates of successful drug developments conditional on a variety of predictive factors known to affect the likelihood of approval, such as the properties of the drug compound, the design of the clinical trial, the results of earlier trials, and the track record of the sponsor. A great benefit Machine Learning models offer is the information scientists, doctors and pharmaceutical professionals on which factors determine the effectiveness of clinical trials which would then lead to optimising this process. Machine Learning predictions would also be helpful to regulators and policymakers, especially for drugs that are likely to fail; in these situations, the most difficult problems in biomedicine are highlighted, and a stronger commitment from the public sector and charitable organisations is called for (Lo, Siah, and Wong, 2018).

3.2.1 Random Forests and Statistical Imputation

The first proposed method we shall introduce is a Random Forest (RF) model employing data from clinical trials and drug development from 2003 to 2015, containing thousands of drug–indication pairs with more than 140 attributes across 15 disease groups (Lo, Siah, and

Wong, 2018). We note that a "drug–indication" pair is referring to the use of a certain drug in treating a particular disease. A common issue with all historical drug development datasets is that they have missing data due to researchers only disclosing a portion of the details of clinical trials and upcoming treatments in order to preserve trade secrets or simply because they had no motivation to do more. For this reason, implementing imputation techniques that let us fully utilise the full dataset is required. Before providing the results of the original article, we give a brief introduction of RF and the imputation method used in the article.

The building block of a Random Forest is a Decision Tree. A Decision Tree is a simple model that aims to partition the feature space into smaller subsets, so that the resulting groups are as different from each other as possible. An example can be seen in Figure 3.1, where a patient is split into subsets based on whether they experience dizziness and subsequently whether their systolic pressure is between $[130, 135]$ or $(135, 140]$. Each of these classifications, leads to the patient receiving different medication.

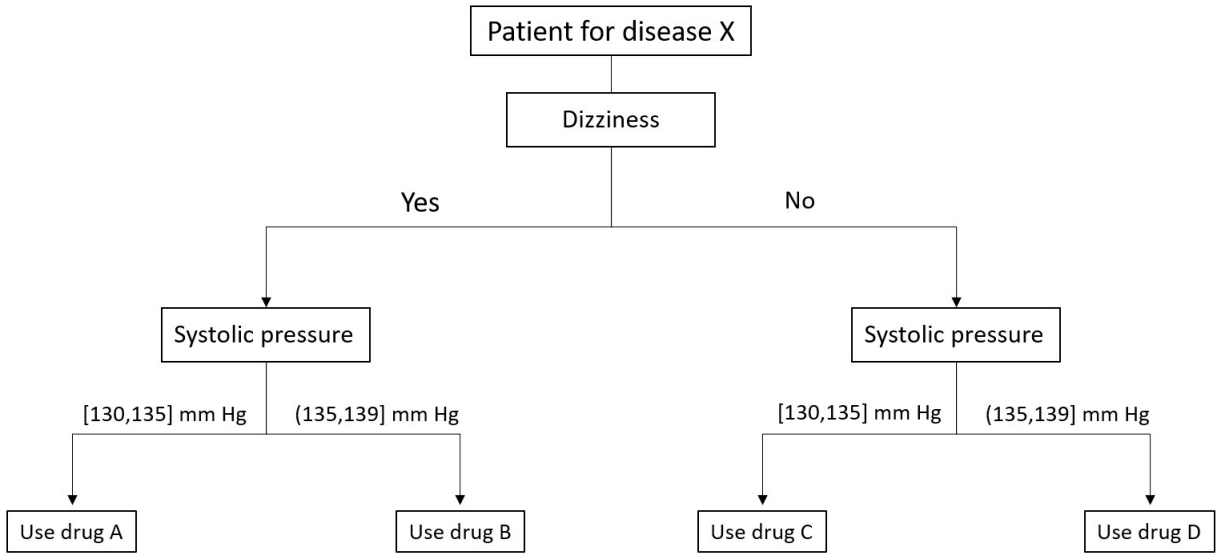

Figure 3.1: Visualised example of a Decision Tree

RF is an ensemble learning algorithm that can be used for both classification and regression (Breiman, 2001). It combines a number of Decision Trees and averages their predictions to produce the final output and has shown to have excellent performance in several situations (Biau and Scornet, 2016). The reason for good performance is an idea called bootstrap aggregation (bagging).

Assuming that we have data $\{(x_i, y_i)\}_{i=1}^n$, we create B bootstrap samples, that is, samples with replacement of size n and fit each individual Decision Tree, $\hat{f}^b(x)$ (predictor) on the resampled data. Then the bagged estimator is just the average of these predictions $\hat{f}_{bag}(x) = \frac{1}{B}\sum_{b=1}^{B} \hat{f}^b(x)$. Although the interpretability of a Random Forest is not as good as a single Decision Tree, bagging reduces variance, prevents overfitting and usually improves performance in practice. Additionally, normally in a Decision Tree for each split point, every

potential feature is taken into account (in Figure 3.1, Dizziness, Systolic Pressure), and the one that creates the greatest gap between the observations is selected, however for Random Forests only a random subset of features is considered. In the end, this leads to less correlation between different Decision Trees and increased diversity by forcing even more variety across the model's trees. Another benefit of Random Forests, which as we shall later see, the authors used, is the ability to calculate variable importance which can give insights to decision makers on what to focus on in order to increase success.

Returning to the previously discussed article, the authors in (Lo, Siah, and Wong, 2018) created the largest datasets (to their knowledge) of drug–indication pairs, one for Phase II to approval and the other for Phase III to approval, both of which span a variety of areas. For both of these datasets several imputation methods were considered together with several Machine Learning algorithms, and the area under the receiver operating characteristic curve (AUC) was used to measure each model's performance and in the end the best performing combination was reported. It turns out that the combination of k–Nearest Neighbor (kNN), where $k = 5$ and RF approach performed the best if one takes into consideration its ease of implementation and application. For completeness, we state that kNN imputation is a method in which the missing value in the dataset is replaced with the mean value from the k samples "closest" (with regard to some distance, e.g., Euclidean) to it.

To summarise the authors' findings, they argue that using their trained classifier, one can distinguish between potential candidate treatments with high and low potential. We note here that the authors were testing for successful advancement to later clinical stages, however this is only a necessary but not a sufficient condition for approval. Additionally, interestingly they computed each feature's importance over all their experiments and found out that trial status (whether the trial was completed or discontinued) and trial outcome (if the trial was completed with its primary endpoints met) are found to have strong relationships with success, were consistently ranking amongst the top two important features. This result is not surprising, as a trial that was discontinued will more likely than not fail to advance to the next Phase and treatments that achieve positive outcomes have a stronger chance of succeeding.

Furthermore, the top ten important variables also included sponsor track records and trial features such as accrual rate, duration, and number of identified locations. The intuition behind the predictive power of the variables can be explained in many ways. For example, trials that conclude quickly without attaining their primary goals, may reduce their chances of being successful, and medications with limited accrual in their trials, which results in low statistical power, may have a lesser chance of being authorised. Additionally, a good track record from a sponsor showcases greater expertise in drug development. Insights such as these contain useful information that, combined with access to higher quality data, can be used when creating other more powerful drug development prediction models which have not yet been considered (Lo, Siah, and Wong, 2018). Additionally, it is important to note that some of the relationships discovered may not necessarily be causal in nature. For instance, a trial may use a particular design because researchers are concerned about the likelihood of success based on a simpler design, so the finding that a complicated design was linked to lower success

would not imply that a simple design would perform better and vice versa.

3.2.2 The ANDI scoring metric

Another useful tool to improve the decision–making of the drug portfolio was taken up by (J. DiMasi et al., 2015), where they tackle the problem from a different point of view. Motivated by APGAR (Apgar et al., 1958), a simple algorithm in which the condition of each newborn is represented by a score, which is the sum of five integers determined within 60 seconds of the baby's entire delivery, the authors proposed Approved New Drug Index (ANDI) to predict regulatory approval for novel cancer treatments following Phase II testing. The idea was to create a tool that would be superior to intuitive decision–making in the following ways:

- decrease bias from decision–making;
- if necessary, prioritises predictive factors based on underlying probability;
- reduces the work required for candidates with a low predicted probability of succeeding and speeds up the rejection of those candidates;
- when only one project is being considered at a time, enables for comparison to certain industry norms.

In addition to having high accuracy, the authors wanted the model to be as interpretable and easy to use as possible.

By creating a dataset related to the clinical development and approval of newly formulated cancer drugs, the goal was to identify variables with high predictive power. They covered a broad list of features that can be roughly divided into four categories: the properties of the molecule itself, economic variables relating to potential markets for the compounds, and the size of the company developing the compound, characteristics of the trial design, and the outcomes of the safety and efficacy tests. The authors then used methods from Machine Learning and statistical inference and combined the results to create ANDI.

Among the different Machine Learning algorithms used to identify the highest predictive variables, RF classification was the best performing model, and was used throughout the analysis. Using an algorithm called RF Recursive Feature Elimination (RF–RFE) (Granitto et al., 2006) they created a well performing RF classification model. RF–RFE is an algorithm where a RF model is trained using all available predictors, model performance is calculated, predictor importance is ranked according to the significance of the RF variables (which we have mentioned is possible with RF) and then the least significant predictor is removed. Then, using the smaller set of predictors, the procedure is repeated until only one predictor remained. The final predictor subset is chosen based on the best–performing model, the predictors of which were given the highest priority for inclusion in the ANDI scoring system.

In addition to that, non–parametric χ^2 tests of association were used to identify which variables had statistically significant association with regulatory success. However, in a multivariate situation like this, not all of these factors function as useful predictors. For this

reason, using a logistic regression that linked variables to the probability of regulatory success, the authors identified which variables, when taken together, offered a useful foundation for predictive purposes.

Considering the outcomes of the Machine Learning and statistical analyses mention above, ANDI index was created by summing the scores for four predicted parameters, results of the randomised Phase II trial (activity), Phase II trial size, a prevalence–like metric (number of patients treated for the primary indication globally), and the length of Phase II testing. Each parameter receives a score from 0 to 2 based on specific cutoffs details for which can be found in the original paper.

Their results show that ANDI is strongly correlated with regulatory marketing approval, meaning that higher ANDI scores corresponded to higher success rates. The same causality remark, as before, should be made here about the relationship of the variables and market approval. Having said that, the authors' recommendation is that the scoring algorithm should be utilised in combination with conventional success rate indicators and factors unique to the compound in question, rather than being applied robotically to determine "go"/"no–go" choices for drugs under development. Adopting such an algorithm–based approach to gain insights on the success probability may guide resources toward drugs for which support is sensible and limit irrational risk–taking that uses significant research and development budgets.

3.3 The Markov Decision Process Approach

The next approach we shall consider is based on a Markov Decision Process (MDP). The nature of the problem makes the use of MDPs a natural modelling possibility, and it is not surprising that it has recently started to be used in the context of clinical trials (Tian, Han, and Powell, 2022; Williamson, Jacko, Villar, et al., 2017).

Generally speaking, decision makers in clinical trials need to consider several decisions during the multi–year development process of a new drug. For example, what sample size should a Phase II trial have? Shall a Phase II trial include interim analyses? Shall the development of the drug continue to Phase III on the basis of current data? These are just a few of the possibilities and in a multi–billion industry such as the pharmaceutical sector we can imagine that these decisions require to be formal and data–driven.

3.3.1 Defining a Markov Decision Process

In this subsection, we are going to give a brief introduction to Markov Decision Processes (MDP). We note here that we give the MDP formulation for a general two–armed problem (following the survey (Jacko, 2019)), which is usually what we would use in the context of clinical trials since a traditional RCT has two arms; any extension to that is easily derived. A Markov Decision Process model contains the following (Tian, Han, and Powell, 2022):

- A set of possible environment states $\boldsymbol{x}$;

- A set of possible actions in that environment $a \in \mathcal{A}$;
- A real valued reward function $R(s, a)$, or an objective function for the optimisation procedure $\mathcal{F}(s, a)$;
- A set of transition probabilities h, which indicates the effect of each action at every state;

In the context mentioned above, we shall consider two arms labelled $k \in \mathcal{K} := \{C, D\}$, where each patient must be assigned to exactly one arm and that patient will provide a binary response $o \in \mathcal{O} := \{0, 1\}$, where 0 (failure) and 1 (success).

Subject responses are stochastic, modelled as Bernoulli distributed with a success probability parameter $0 \leq \theta_k \leq 1$ that is independent of the arm. The responses are instantaneous, which means that it is possible to observe a subject's response before making the following decision.

At random moments in continuous time, subjects are recruited one by one. These arrival times, which from now on we will refer to as time (or decision) epochs are distinct and regularly spaced. These time epochs are the moments in time where we have to decide to which treatment the arrived subject will be allocated. In more mathematical notation, we can think of subjects as arriving at the time epochs $t \in \mathcal{T} := \{0, 1, \ldots, T-1\}$ where $T \leq +\infty$ is the total number of patients, also known as the time horizon. To avoid confusion, the patient arriving at time epoch t is the $(t+1)$–st of the trial.

At any moment, every piece of information that can affect the next decision is collected in a vector, which we refer to as state, which is divided into the physical and information states. The physical state contains information about the physical properties of the system or available assets of the experiment. In our context, the physical state is represented by the number of observed successes and failures for each arm, the number of subjects assigned without an observed response for each arm, the number of subjects that arrived, but were not still assigned to any arm, and the number of subjects still to arrive. However, since decisions are made at time epochs, we focus our attention on those, which simplifies the physical state to just five components, the numbers of observed successes and failures in both arms denoted by s_C, s_D, f_C, f_D, respectively, and the number of subjects awaiting arrival, n. Because $s_C + s_D + f_C + f_D + n = T$, where T is known, we can choose any four of these numbers to monitor, and for the purposes of this introduction, without loss of generality we choose $\boldsymbol{x} := (s_C, f_C, s_D, f_D)$.

We mentioned before that along with the physical state, there is also an information state $\boldsymbol{i}$, which at any one point in continuous time gathers all the information that could influence the next decision. Real–world evidence or modeling assumptions may be included in this. Real–world evidence might be introduced at any time during the trial, or it might be available before it begins. The modelling assumptions usually refer to the prior distributions and the parameters used for the success probability of each arm (this typically is based on historical data or expert opinions), but may also incorporate additional factors like the likelihood of dropouts, the timing of planned interim analyses, the degree of randomisation between the two treatments, the cost of acquiring a new subject, the likelihood and timing of an unplanned

trial termination due to safety reasons, the estimated size of the subject population after the trial, to name a few. The full state vector is given by $(\boldsymbol{x}, \boldsymbol{i})$

The goal of a Markov Decision Process is to calculate an optimal policy $\pi \in \Pi$ for the environment, meaning that at each time epoch $t \in \mathcal{T}$ we ought to choose to interact with the environment by picking the optimal action based on the current state (Markov Property). In this context, we need to decide how the arriving subjects will be randomly assigned to each of the arms. These randomised actions a correspond to probabilities (p_C^a, p_D^a), which means that under action a the subject who arrives is assigned to the corresponding treatment with the respective probability. Formally, we define the action set $\mathcal{A}_{(\boldsymbol{x},\boldsymbol{i})} \subseteq \{a : p_C^a \geq 0, p_D^a \geq 0, p_C^a + p_D^a = 1\}$. The Markov Decision Process theory states that an action which is a randomised combination of the other two actions is optimal only if all three are optimal, thus it is sufficient to consider only an action set of two pure randomized actions $a = 1, 2$ (Jacko, 2019). In the case where both actions are optimal, we resolve this by considering a third action $a = 3$, an equally–weighted mixed randomized action, which is given by $(p_C^3, p_D^3) = ((p_C^1 + p_C^2)/2, (p_D^1 + p_D^2)/2)$.

Next, we define the transition probability for any time epoch. Let $q_{k,(\boldsymbol{x},\boldsymbol{i}),o}$ denote the probability of observing response $o \in \mathcal{O}$ for a subject allocated at arm $k \in \mathcal{K}$ in state $(\boldsymbol{x}, \boldsymbol{i})$. Assuming the information $\boldsymbol{i}$ stays the same during the whole trial (otherwise minor changes are needed), and that there are no missing responses, then the transition probability from state $(\boldsymbol{x}, \boldsymbol{i})$ to state $(\boldsymbol{x}', \boldsymbol{i})$ under the selected action a is,

$$h^a_{(\boldsymbol{x},\boldsymbol{i}),(\boldsymbol{x}',\boldsymbol{i})} = \begin{cases} p_C^a q_{C,(\boldsymbol{x},\boldsymbol{i}),1}, & \text{if } \boldsymbol{x}' = \boldsymbol{x} + \boldsymbol{e}_1 \\ p_C^a q_{C,(\boldsymbol{x},\boldsymbol{i}),0}, & \text{if } \boldsymbol{x}' = \boldsymbol{x} + \boldsymbol{e}_2 \\ p_D^a q_{D,(\boldsymbol{x},\boldsymbol{i}),1}, & \text{if } \boldsymbol{x}' = \boldsymbol{x} + \boldsymbol{e}_3 \\ p_D^a q_{D,(\boldsymbol{x},\boldsymbol{i}),0}, & \text{if } \boldsymbol{x}' = \boldsymbol{x} + \boldsymbol{e}_4. \end{cases}$$

where the vector $\boldsymbol{e}_j$ is the usual basis vector.

Finally to identify the optimal policy we need to introduce the expected one–period reward. This in turn leads to an overall expected return of a state, which we are interested in optimising. For a given set of state $(\boldsymbol{x}, \boldsymbol{i})$ and action a, the expected one–period reward is defined as $r^a_{(\boldsymbol{x},\boldsymbol{i})} = p_C^a q_{C,(\boldsymbol{x},\boldsymbol{i}),1} + p_D^a q_{D,(\boldsymbol{x},\boldsymbol{i}),1}$.

3.3.2 Recent Work of Markov Decision Processes In Clinical Trials and Healthcare

Based on the above overview of MDPs, it is evident that MDPs fit quite naturally in the context of clinical trials, especially adaptive clinical trials. A clinical trial can get quite complex and many decisions need to be made, as we have already mentioned. The aforementioned, combined with the fact that COVID–19 has fundamentally changed clinical trials and made us rethink over 70 years of practice (Park, Mogg, et al., 2021) is why we believe that MDPs have recently started to be widely used in healthcare and clinical research articles, and will continue to do so, especially in the context of decision making in clinical trials. In what follows, we

present some of the existing recent work to give an idea to the reader of what has been done.

First, (Kouvelis, Milner, and Tian, 2017) take a for–profit firm perspective with the goal of increasing the anticipated net present value of a treatment based on the costs of running the trial, the likelihood that the drug will be approved, which is moderated by its quality, and the estimated revenue stream provided that the drug is approved. Their model connects trial results to a theoretical framework which determines the timing and number of test sites that should be opened as well as the optimal rate at which patients should be enrolled in Phase III clinical trials.

From the same profitability point of view, (Rojas-Cordova and Bish, 2018) developed a model used for adaptive Phase III clinical trials with interim analyses points and treatments with binary response. Their model maximises the firm's expected profit from a new drug by determining the optimal patient enrolment and trial termination policy while accounting for the probability of efficacy of the treatment.

Next, (Alban, Chick, Forster, et al., 2020) instead of focussing on uncertainties in patient enrolment, they worked to increase the effectiveness of the health & technology innovation process by optimising both the duration of the trial and the recruitment rate within various regulatory and practical contexts. More specifically, they provided a model for a two–armed clinical trial in which the trial's recruitment rate and duration are both optimised. They do this by balancing the trial's cost with the added benefit for patients and the target population, measured by the respective health benefits and costs of the technologies.

The authors in (Williamson, Jacko, Villar, et al., 2017) looked at a more specific problem occurring in rare disease clinical trials. Rare disease clinical trials have a main difference from typical clinical trials, in the sense that the trial may involve a sizable fraction of the population who has the condition. This means that we should account for that and focus on providing the most effective care for those participants in the trial, while balancing this with learning about a treatment's efficacy. They provide a novel randomised response–adaptive design that maximises the overall number of patient successes in the trial and penalises if a required number of patients are not included in each treatment arm, with the added benefit of improving the power of the trial which is known to occur in practice, when working with adaptive designs. Recently, they extended their previous work (Williamson, Jacko, and Jaki, 2022) by providing a generalisation to the model that was prompted by the practicalities of clinical trials, e.g. delayed responses.

Another common design for clinical trials is interim analysis in clinical trials, as we have mentioned. This led (Tian, Han, and Powell, 2022) to focus on this type of trial and find the optimal patient enrolment for investment purposes, while learning about drug quality. Their model is adaptive and takes into account the efficacy of treatments and the uncertainties in patient enrolment at the specified interim analysis points. This in turn affects clinical trial operations and potential revenue for investors. They also provided insights into how finishing a study early and accelerating a trial affects the net present value of the drug's earnings.

In the following Chapter, we present our contribution to the field by giving a novel model that operates within the MDP framework.

Chapter 4

Optimal Decision-Making with a Markov Decision Process

In this Chapter we present a novel model which we hope will help in the decision–making of clinical trials and will act as a good foundation for a more complete future model. Unlike the previous works, our model will focus on finding the optimal combination of Phase II and Phase III clinical trials to maximise overall patient successes. The first model uses some simple assumptions but the goal as we shall see is to extend this to a more complex model that can be used in a broader set of scenarios.

4.1 Selecting the Optimal Combination of Phase II - Phase III Designs

Assume we have $k = 1, \ldots, K$ different one–armed Phase II designs, with a binary endpoint for a treatment D. We assume that each trial k has corresponding trial size T_k. At $t = 0$, we assume that the treatment effect can be modelled as a Bernoulli distribution, that is,

$$X \sim \text{Bernoulli}(1, \theta_{D,0}),$$

where $\theta_{D,0}$ is an unknown success probability. A sensible prior distribution for the treatment effect is a Beta distribution, i.e. $\theta_{D,0} \sim \text{Beta}(s_0, f_0)$, where (s_0, f_0) are considered "pseudo" observations, usually based on Phase I data. Our goal is to pick the optimal Phase II design out of the K different ones. The action set $\mathcal{A}_0$ is constant, $|\mathcal{A}_0| = K$, identified by choosing one of the K different Phase II designs, where the subscript is added to emphasise the time epoch $t = 0$.

We are going to introduce the state vector step by step. We initially have real observations of the Phase II trial s_1, f_1. At $t = 0$, we just have $\boldsymbol{z} = (s_1, f_1) = (0, 0)$. The transition probability from state $(0, 0)$ to any other possible state, given that we chose the action a, is calculated through the posterior predictive pmf $G_0^a \sim \text{Beta-binomial}(T_a, s_0, f_0)$, where s_0, f_0 are prior parameters. The Beta-binomial distribution is a kind of Binomial distribution in which instead of having a fixed success probability, we use a Beta distribution as a prior for the probability of success.

The expected one period reward for this time period is given by,

$$\mathcal{R}_0^a(\boldsymbol{z}) = -T_a \cdot \theta_C - T_a \cdot c = -T_a \cdot (\theta_C + c) \tag{4.1}$$

where θ_C is a well known quantity indicating the effectiveness of the existing treatment C, thus $-T_a \cdot \theta_C$ is the "lost" expected number of successful treatments from patients who

would have received the existing treatment C rather than the new treatment and c is the cost of recruiting one patient for the trial, thus $-T_a \cdot c$ is the cost of acquiring T_a patients. For completeness, we state that for this definition we implicitly assume that patients not receiving treatment D, would receive treatment C.

At $t = 1$, we learn the outcome from the chosen Phase II trial and choose whether we will continue or not to the Phase III trial. The current state values (s_1, f_1) are used to inform our prior for Phase III. We denote $s_{2,C}, s_{2,D}$, the successes for both treatments during the Phase III trial, and thus $\boldsymbol{z} = (s_1, f_1, s_{2,C}, s_{2,D})$. We also note that we assume no information is gained from the Phase II trials we did not join (this can later be relaxed).

The decision we need to make at $t = 1$ is whether to continue with a Phase III trial or not, so the set of actions $\mathcal{A}_1$ is again constant, $|\mathcal{A}_1| = 2$, where each action corresponds to carrying out or not carrying out ("go"/"no–go" decision) the Phase III trial. For the Phase III trial, we assume the typical fixed sample size, which can depend on (s_1, f_1), 1:1 allocation, two–armed trial. The possible interventions are labelled by $k \in \{C, D\}$, corresponding to control and discovery. Let the quality means of drug C and D be θ_C, θ_D, respectively.

The aim of a Phase III trial is to test the hypothesis of whether the new treatment D is significantly better than the treatment currently used or the placebo treatment, C, that is,

$$H_0 : \theta_D = \theta_C, \quad vs \quad H_1 : \theta_D > \theta_C,$$

which will be tested using Fisher's exact test (Sprent, 2011). We assume a significance level of $\alpha = 2.5\%$ and power $1 - \beta = 80\%$ and assume that the minimal clinically relevant difference is $k = 20\%$. Let n be the sample size required to achieve such power and Type I error. Let p_D, be the proportion of subjects cured by treatment D calculated from the Phase II trial and p_C be the proportion of subjects cured by treatment C, which is well–known. To calculate the required sample size we use the following frequentist formula, (Sakpal, 2010),

$$n = \frac{(z_\alpha + z_\beta)^2 \cdot [p_C(1 - p_C) + p_D(1 - p_D)]}{k^2}. \tag{4.2}$$

The transition probability at $t = 1$ for drug D is computed using posterior predictive pmf $G_{1,D} \sim$ Beta-binomial$(n/2, s_{1,D}, f_{1,D})$, where $s_{1,D} = s_1 + s_0, f_{1,D} = f_1 + f_0$, where s_1, f_1 are the successes and failures, respectively, observed at the end of the chosen Phase II trial and indicate how confident we are in our new treatment. Similarly, the transition probability at $t = 1$ for drug C is computed via the posterior predictive pmf $G_{1,C} \sim$ Beta-binomial$(n/2, s_{1,C}, f_{1,C})$, where $s_{1,C}, f_{1,C}$, are well–known quantities.

The expected one period reward for this period is given by,

$$\mathcal{R}_1^a(\boldsymbol{z}) = \begin{cases} s_1 - C \cdot Pop, & \text{if } \ a = 1 \ \text{ (no–go decision)} \quad (4.3a) \\ s_1 - n \cdot c, & \text{if } \ a = 2 \ \text{ (go decision)} \quad (4.3b) \end{cases}$$

where C is the "moral cost" of not developing the new drug for patients with the respective disease, as the assumption is that they do not receive better treatment, Pop is the after–trial patient population that will receive the statistically better new treatment or the current treatment, and R is the revenue from the new drug.

Finally, at $t = 2$ there is no action to be taken; we just observe the results of the Phase III trial. The expected one period reward for this period is,

$$\mathcal{R}_2(\boldsymbol{z}) = s_{2,D} + s_{2,C} + 1_{H_1} \cdot (Pop - n) \cdot R - 1_{H_0} \cdot C \cdot (Pop - n) \tag{4.4}$$

We now introduce the value function, which is going to be used to find the optimal policy π. Let Π be the family of possible decisions we can make. Let $\mathcal{F}_t(\boldsymbol{z})$ be the value function representing the maximum expected total reward, that is,

$$\mathcal{F}_t(\boldsymbol{z}) = \max_{\pi \in \Pi} \mathbb{E}^{\pi} \left[\sum_{\tau=t}^{2} R_{\tau}^{a(\tau)}(\boldsymbol{z_\tau}) \middle| \boldsymbol{z_t} = \boldsymbol{z} \right]. \tag{4.5}$$

The optimisation problem in Equation 4.5 can be solved exactly using dynamic programming methods. This solution results in the best combination of Phase II and Phase III designs. More specifically, we use a method called backward induction, a technique which starts at the end, calculates the reward for every possible combination of states, and proceeds iteratively towards the start. We give the details of how this was implemented in R below and give the pseudocode in Algorithm 1. Additionally, the R code can be found in the following repository: `https://github.com/NikosTsikouras/MRes-thesis`.

We start at $t = 1$ and find every possible combination of successes and failures (s_1, f_1), for every Phase II sample size T_a. After that, we move to $t = 2$ and calculate the reward for each combination of successes for the respective treatment $s_{2,C}, s_{2,D}$, using Equation 4.4. Then, we go back to $t = 1$, and for each (s_1, f_1) we calculate the expected reward under each decision, "go" or "no–go". For the "go" decision, we do this by summing over the rewards at $t = 2$ weighted by the respective transition probability and adding Equation 4.3a. For the "no–go" decision, we do this by summing Equation 4.3b for every possible combination of states.

To find the optimal action, we then compare the expected reward under a "go" decision to the reward associated with "no–go", and take the action that maximises the expected reward as the optimal action associated with (s_1, f_1), say $R(s_1, f_1)$.

After that, we move back to $t = 0$ and calculate the expected reward associated with each Phase II design, say k, by adding Equation 4.1 to $R_k = \sum_{s_1, f_1} R(s_1, f_1) \cdot \mathbb{P}\left(\text{reaching state}(s_1, f_1) | (s_0, f_0)\right)$, where the sum is over all possible combinations (s_1, f_1) for the particular design k. The decision maker is then able to choose which of the Phase II candidate designs is optimal by taking the one that maximises the expected reward, that is, choose the design: $\arg\max_k R_k$.

To our knowledge, this work is the first to look at the optimal combination of Phase II – Phase III designs. We certainly believe that, there is more research to be done around the area, as there is a great potential of reducing the cost of the development of novel treatments and help decision makers make more rational choices. This could potentially (and ideally) help reduce "Eroom's Law", which states that the cost of creating new treatments doubles roughly every nine years (Scannell et al., 2012).

Algorithm 1 Backward induction for solving the Equation 4.5

Require: $s_0, f_0, s_{1,C}, f_{1,C}, \alpha, \beta, k, p_C, \theta_C, Pop, R, c,$, Phase II designs (K)

for k in K **do**
    Find every possible combination of (s_1, f_1), say L_k
end for
for k in K **do**
    for (s_1, f_1) in L_k **do**
        Find n using Equation 4.2
        Find $\mathcal{R}_2(\boldsymbol{z})$ using Equation 4.4
    end for
end for
for k in K **do**
    for (s_1, f_1) in L_k **do**
        Find $\mathcal{F}_1(\boldsymbol{z})$ using $R_2(\boldsymbol{z})$, Equations 4.3a,4.3b and the probability density functions of $G_{1,D} \sim$ Beta-binomial$(n/2, s_{1,D}, f_{1,D})$, and $G_{1,C} \sim$ Beta-binomial$(n/2, s_{1,C}, f_{1,C})$
    end for
end for
for k in K **do**
    for (s_1, f_1) in L_k **do**
        Choose the action $a = 1, 2$ that maximises $\mathcal{F}_1^k(\boldsymbol{z})$ associated with state (s_1, f_1).
    ▷ Note we added the superscript to emphasise the Phase II trial
    end for
end for
for k in K **do**
    for (s_1, f_1) in L_k **do**
        Find $\mathcal{F}_0^k(\boldsymbol{z})$ using $\mathcal{F}_1^k(\boldsymbol{z})$, Equation 4.1, and the probability density function of $G_0^k \sim$ Beta-binomial(T_k, s_0, f_0)
    end for
end for
for k in K **do**
    Take action $a = 1, \ldots, K$ that maximises the expected reward, i.e. choose $\arg\max_k \mathcal{F}_0^k(\boldsymbol{z})$
end for
return Optimal Actions at $t = 1$ and $t = 2$ for all possible states

4.1.1 Numerical Experiments in Simulated Scenarios

In this subsection, the aim is to highlight the usefulness of our model in different simulated scenarios. We aim to identify useful insights from the scenarios which would ideally provide ideas for further work.

4.1.1.1 Slightly Better Novel Treatment

For this scenario, we are testing a novel treatment which is slightly superior to the control treatment. We assume that the control treatment has an effectiveness of $p_C = 0.4$, while the novel treatment has a true (in practice unknown) effectiveness of $p_D = 0.6$. We note that the novel treatment is just on the boundary of having the prespecified clinically relevant difference $k = 0.2$. To find the corresponding prior distribution values (s_0, f_0), we assume a sample size of 20 Phase I subjects which is common (Garrett-Mayer and O'Connell, 2018), and use R to simulate them. The resulting parameters are $(s_0, f_0) = (13, 7)$. The corresponding prior parameters for the treatment effect C are $(s_{1,C} f_{1,C}) = (350, 520)$, indicating high certainty (small variance) around the value of p_C. We use as is common in practice $\alpha = 0.025, \beta = 0.2$ and $k = 0.2$. For the possible Phase II designs, we use the following sample sizes $K = \{30, 40, 50, 60, 70, 80\}$. Finally, we use the average cost to recruit a patient which is roughly $c =$£$6,500$ (Moore et al., 2018), $C = 0.005$ (which is hard to quantify in practice) and an after trial patient population $Pop = 5.000.000$. A summary of all these values can be found in Table 4.1.

p_D	p_C	s_0	f_0	$s_{1,C}$	$f_{1,C}$	α	β	k	c	R	Pop	C
0.6	0.4	13	7	350	520	0.025	0.2	0.2	£6,500	500	5.000.000	0.005

Table 4.1: Values for the first experiment of slightly better novel treatment ($p_D = 0.6$ and $p_C = 0.4$).

The resulting optimal decisions ("go"/"no–go") for every combination of (s_1, f_1) given all Phase II sizes are summarised in Figure 4.1. We see that as expected, as the successes (s_1) at the end of Phase II are increasing, we have more "go" decisions, which is intuitive as a larger number of successes is indicative of a better treatment D. We note that around $61\% - 63\%$ of decisions at $t = 1$ are "no–go", details can be found in Table 4.2.

Furthermore, the resulting optimal decision (choice of Phase II sample size) is $k = 60$, with an expected final reward of £416.7 million; details can be found in Table 4.2. The intuition behind this is that with a "smaller" increase in effectiveness (in this scenario, 0.2), we would need a "larger" Phase II sample size to showcase it. We emphasise that the rewards in Table 4.2 are the expected final rewards, which means that there is the possibility of reaching an unfavourable state and mistakenly failing to proceed to Phase III, as can be seen in Table 4.4, where the most probable decision for $k = 40$ at $t = 1$ is a "no–go".

Interestingly, in this specific example where the novel treatment is slightly better than the control treatment, we have a probability of around 50%–60% to correctly identify the "go" decision, a detailed summary can be seen in Table 4.3. However, we note that these values are inflated, as in reality, after simulating this scenario for $N = 50$ times using the same parameters as in the original experiment (Table 4.1), we find that the overall probability of correct "go" decision is between 35%–46%, details can be found in Table 4.3. This shows a limitation of our model, which is perhaps understandable, as we have mentioned that the novel treatment effect is barely considered to be at least greater than the clinically relevant difference k. We address this limitation in the next Chapter.

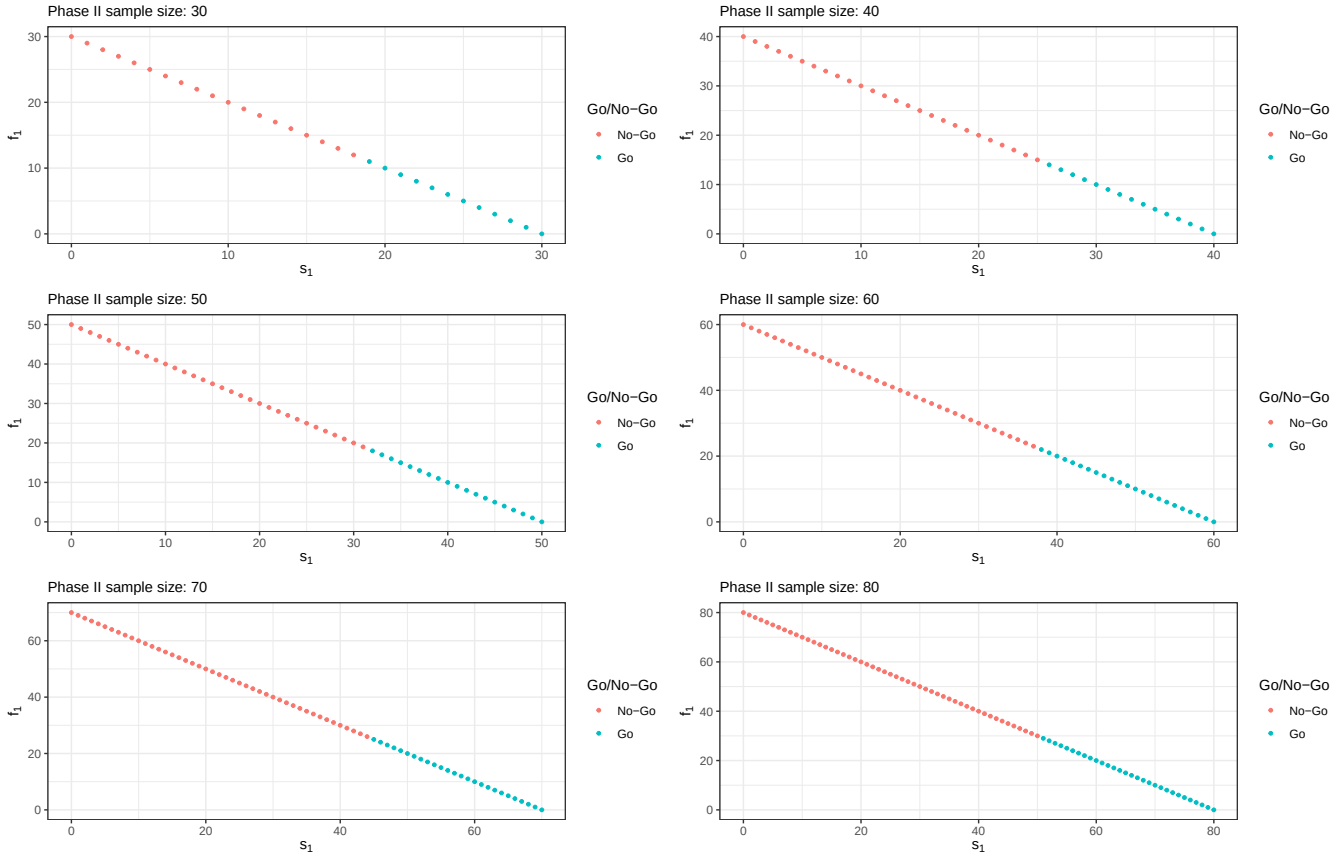

Figure 4.1: Optimal decisions ("go"/"no–go") for all combinations (s_1, f_1) given Phase II sizes for the first experiment ($p_D = 0.6$ and $p_C = 0.4$).

Phase II sample size	% of "no–go" decisions	Expected reward
30	0.613	£412,1m
40	0.634	£414,7m
50	0.627	£415,2m
60	0.623	**£416,7m**
70	0.634	£414,4m
80	0.630	£406,1m

Table 4.2: Percentages of overall "no–go" decisions (at $t = 1$) and expected final rewards (at the start of the trial, $t = 0$) for the different Phase II sample sizes for the first experiment ($p_D = 0.6$ and $p_C = 0.4$).

4.1.1.2 Clearly Better Novel Treatment

For this scenario, we are testing a novel treatment that is clearly superior to the control treatment. We assume as previously that the control treatment has an effectiveness of $p_C =$

Phase II sample size	Prob. of "go" decision	Overall prob. of correct choice
30	0.612	0.35
40	0.557	0.45
50	0.580	0.42
60	0.597	0.42
70	0.565	0.46
80	0.580	0.40

Table 4.3: Probability of correct "go" decisions (at $t = 1$) for the example mentioned in the text and overall probability of correct "no-go" choice of our model after simulating $N = 50$ scenarios for the different Phase II sample sizes for the first experiment ($p_D = 0.6$ and $p_C = 0.4$).

Phase II sample size	Most probable state-decision at $t = 1$
30	(20,10) - Go
40	(25,15) - No–Go
50	(33,17) - Go
60	(40,20) - Go
70	(47,23) - Go
80	(53,27) - Go

Table 4.4: Most probable state and decision at $t = 1$ for the different Phase II sample sizes for the first experiment ($p_D = 0.6$ and $p_C = 0.4$).

0.4, while the novel treatment has a true effectiveness of $p_D = 0.8$. Following the procedure we mentioned in the previous subsection we find $(s_0, f_0) = (17, 3)$. Again, the corresponding prior parameters for the treatment effect C are $(s_{1,C}, f_{1,C}) = (350, 520)$, and we use $\alpha = 0.025, \beta = 0.2$ and$k = 0.2$. For the possible Phase II designs, we used the following sample sizes $K = \{30, 40, 50, 60, 70, 80\}$. Finally, we used $c =$£$6,500$, $C = 0.005$ and an after trial patient population $Pop = 5.000.000$. A summary of all these values can be found in Table 4.5.

p_D	p_C	s_0	f_0	$s_{1,C}$	$f_{1,C}$	α	β	k	c	R	Pop	C
0.8	0.4	17	3	350	520	0.025	0.2	0.2	£6,500	500	5.000.000	0.005

Table 4.5: Values for the second experiment of clearly better novel treatment ($p_D = 0.8$ and $p_C = 0.4$).

The resulting optimal decisions ("go"/"no–go") for every combination of (s_1, f_1) given all Phase II sizes are summarised in Figure 4.2. The same remark can be made here, as the successes (s_1) at the end of Phase II are increasing, we have more "go" decisions, which is intuitive since a larger number of successes is indicative of a better treatment D. We note that around $51\% - 59\%$ of the decisions at $t = 1$, are "no–go", details can be found in Table 4.7.

Additionally, the resulting optimal decision (choice of Phase II sample size) is $k = 50$, with an expected final reward of £1,689 million, details can be found in Table 4.7. Intuitively, this is smaller than the previous optimal sample size ($k = 60$), since the novel treatment is clearly better than the control (40% better in this situation, compared to 20% before), and therefore would require a smaller sample size to identify this difference.

All the expected final rewards for every sample size are given in Table 4.7. We note here that the expected reward is approximately 4 times higher than the previous scenario, which is again indicative of the clearly more effective treatment, as overall we have more correctly identified "go" decisions. Another difference to before is that the most probable decision for every Phase II sample size at $t = 1$ is a "go", as can be seen in Table 4.8.

A notable difference is in the probabilities of correctly identifying the "go" decision. In this specific example where the novel treatment is significantly better than the control treatment, we have a probability of over 99% to correctly identify the "go" decision, a detailed summary can be seen in Table 4.6. Again, from a simulation of $N = 50$ using the same parameters (Table 4.5) these values are inflated, as the actual overall probability of correct "go" decision is between 88%–92%, details can be seen in Table 4.6. This is important because it shows the strength of our method of identifying a "go" decision, with high probability, when the difference between treatments is clear.

Phase II sample size	Prob. of "go" decision	Overall prob. of correct choice
30	0.995	0.88
40	0.995	0.92
50	0.995	0.89
60	0.993	0.89
70	0.993	0.91
80	0.991	0.90

Table 4.6: Probability of correct "go" decisions (at $t = 1$) for the example mentioned in the text and overall probability of correct "no-go" choice of our model after simulating $N = 50$ scenarios for the different Phase II sample sizes for the second experiment ($p_D = 0.8$ and $p_C = 0.4$).

4.1.1.3 Worse Novel Treatment

For this scenario, we are testing a worse treatment which is slightly worse than the control treatment. We assume that the control treatment has an efficacy of $p_C = 0.5$, while the novel treatment has a true efficacy of $p_D = 0.45$. The reason for such a small difference is that we want to showcase the strength of our method in correctly identifying a "no–go" decision. Following the procedure we mentioned in the previous subsections we find $(s_0, f_0) = (8, 12)$. The corresponding prior parameters for the treatment effect C are $(s_{1,C} f_{1,C}) = (520, 520)$, again indicating high certainty around the value of p_C, and we use $\alpha = 0.025, \beta = 0.2$ and $k = 0.2$. For the possible Phase II designs, we use as before the following sample sizes

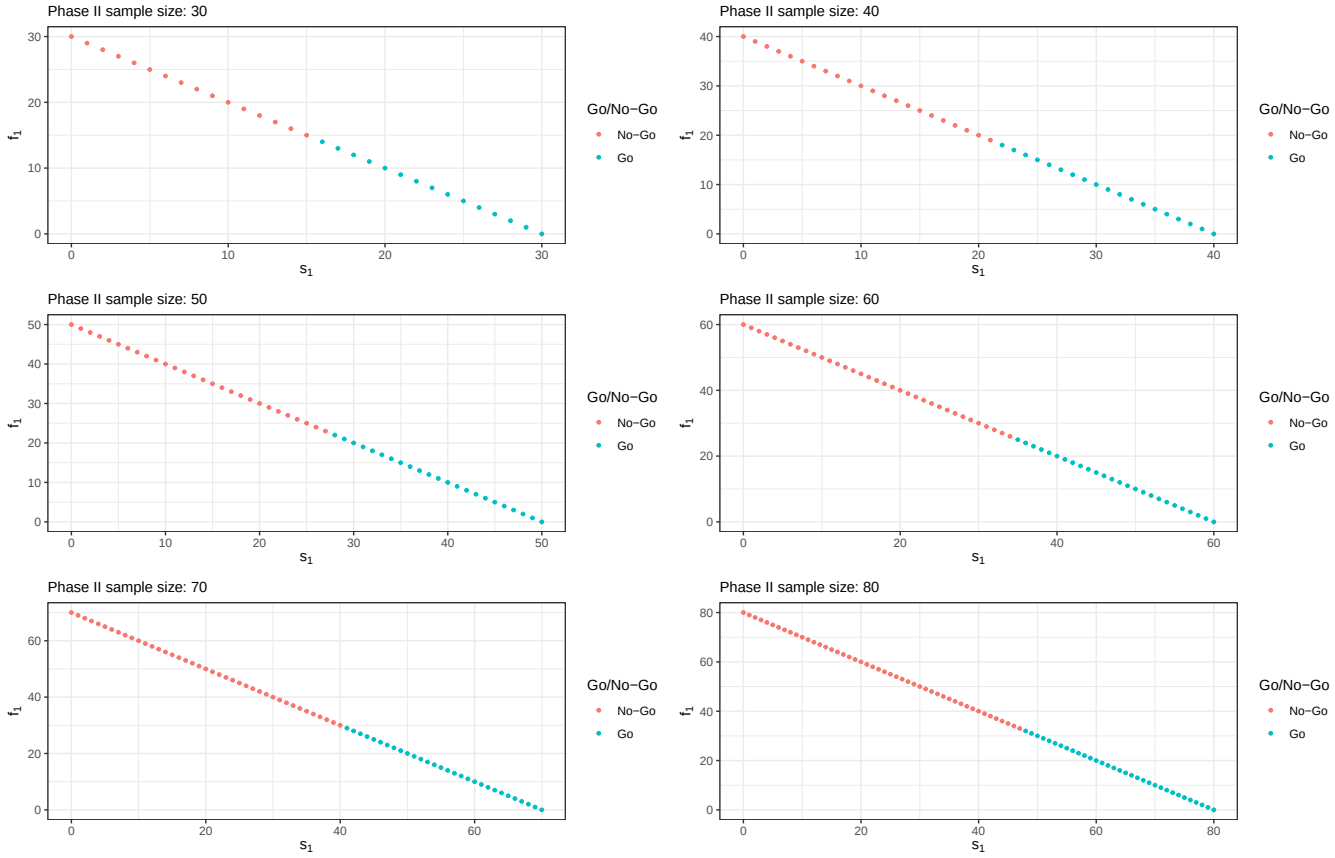

Figure 4.2: Optimal decisions ("go"/"no–go") for all combinations (s_1, f_1) given Phase II sizes for the second experiment ($p_D = 0.8$ and $p_C = 0.4$).

Phase II sample size	% of "no–go" decisions	Expected reward
30	0.516	£1,664m
40	0.536	£1,679m
50	0.549	**£1,689m**
60	0.573	£1,674m
70	0.577	£1,664m
80	0.592	£1,664m

Table 4.7: Percentages of overall "no–go" decisions (at $t = 1$) and expected final rewards (at the start of the trial, $t = 0$) for the different Phase II sample sizes for the second experiment ($p_D = 0.8$ and $p_C = 0.4$).

$K = \{30, 40, 50, 60, 70, 80\}$. Finally, we use $c =$ £$6,500$, $C = 0.005$ and an after trial patient population $Pop = 5.000.000$. A summary of all these values can be found in Table 4.9.

The resulting optimal decisions ("go"/"no–go") for every combination of (s_1, f_1) given all

Phase II sample size	Most probable state-decision at $t = 1$
30	(27,3) - Go
40	(36,4) - Go
50	(45,5) - Go
60	(54,6) - Go
70	(63,7) - Go
80	(72,8) - Go

Table 4.8: Most probable state and decision at $t = 1$ for the different Phase II sample sizes for the second experiment ($p_D = 0.8$ and $p_C = 0.4$).

p_D	p_C	s_0	f_0	$s_{1,C}$	$f_{1,C}$	α	β	k	c	R	Pop	C
0.45	0.5	8	12	520	520	0.025	0.2	0.2	£6,500	500	5.000.000	0.005

Table 4.9: Values for the third experiment of worse novel treatment ($p_D = 0.45$ and $p_C = 0.4$).

Phase II sizes are summarised in Figure 4.3. Here we see that "go" decisions begin to occur for a greater number of successes (s_1) at the end of Phase II, and this happens because of the "not promising" prior parameters (s_0, f_0) generated by the worse novel treatment D.

We note that around $76\% - 84\%$ of decisions at $t = 1$ are "no–go". Furthermore, we note that for every Phase II sample size, the expected final rewards are negative, indicating that the decision makers should consider terminating the trial before Phase II starts, a summary of both can be found in Table 4.10. This choice, of terminating the trial before Phase II starts, can later be added as another feasible choice for our model. However, we note that the optimal decision in this scenario is to use the smallest number of patients for Phase II (i.e. $k = 30$) as this would lead to the smallest amount of loss.

Another noteworthy observation is that, in the case the decision makers continue with the Phase II, which could potentially happen in a situation where risk–taking is more encouraged, our method with almost certainty ($> 99\%$) would give a "no–go" decision as the optimal choice. As previously, the actual probabilities were calculated with a simulation of $N = 50$, using the same parameters (Table 4.9) and the overall probabilities resulting from a correct "no–go" choice range from 94% – 98%, a summary of both can be seen in Table 4.11. This showcases that our method can identify a "no–go" decision, with high probability, when such a decision is optimal, even in a scenario where the two effectiveness of the two treatments is very similar. This is quite significant as a worse novel treatment should by no means transition to a Phase III trial.

For completeness we state that the most probable decision for every Phase II sample size at $t = 1$ is a "no–go", as can be seen in Table 4.12.

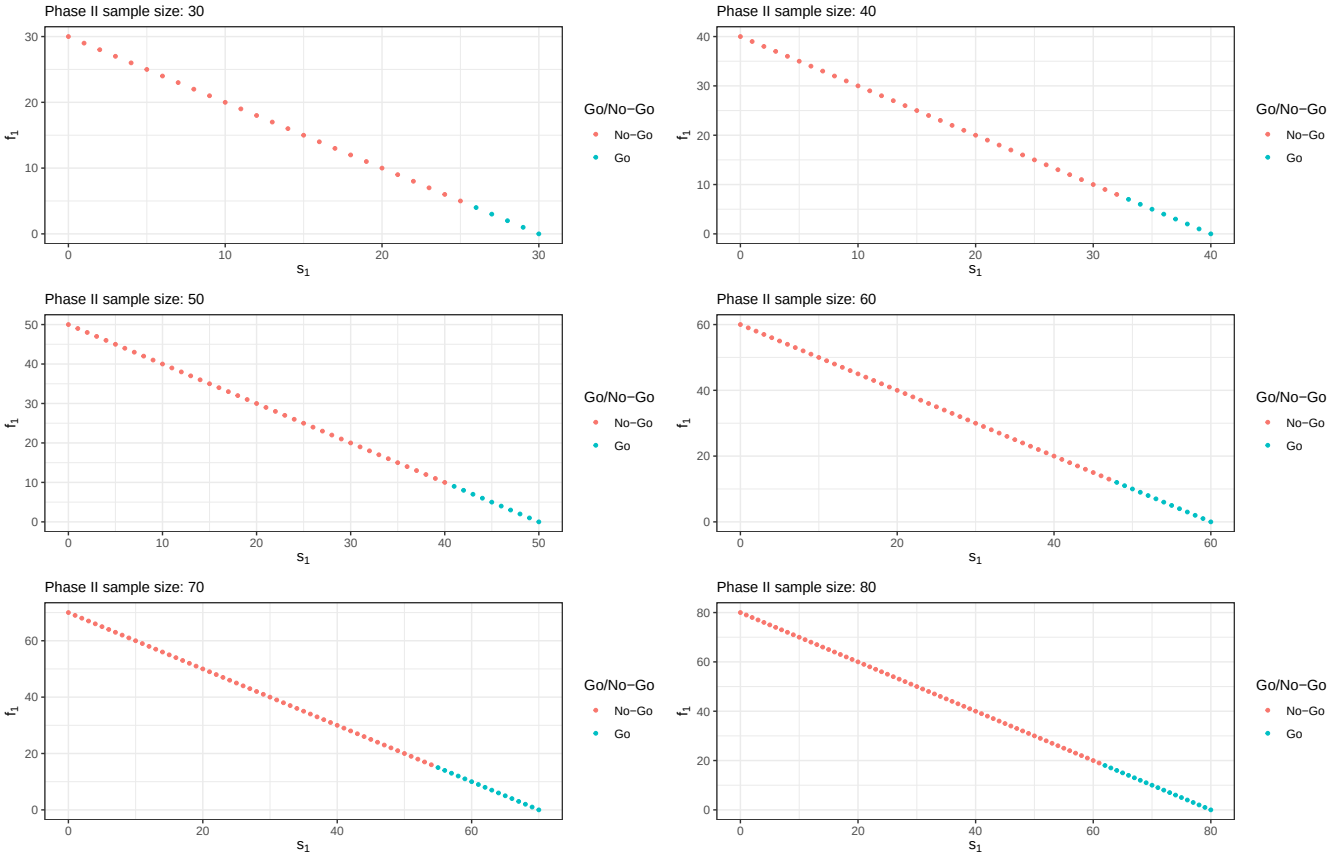

Figure 4.3: Optimal decisions ("go"/"no–go") for all combinations (s_1, f_1) given Phase II sizes for the third experiment ($p_D = 0.45$ and $p_C = 0.5$).

Phase II sample size	% of "no–go" decisions	Expected reward
30	0.838	-£60,9m
40	0.805	-£65,6m
50	0.804	-£71,9m
60	0.787	-£79,1m
70	0.775	-£87,7m
80	0.765	-£97,5m

Table 4.10: Percentages of overall "no–go" decisions (at $t = 1$) and expected final rewards (at the start of the trial, $t = 0$) for the different Phase II sample sizes for the third experiment ($p_D = 0.45$ and $p_C = 0.5$).

Phase II sample size	Prob. of "no–go" decision	Overall prob. of correct choice
30	0.999	0.94
40	0.999	0.98
50	0.999	0.95
60	0.999	0.96
70	0.999	0.97
80	0.999	0.97

Table 4.11: Probability of correct "no-go" decisions (at $t = 1$) for the example mentioned in the text and overall probability of correct "no-go" choice of our model after simulating $N = 50$ scenarios for the different Phase II sample sizes for the third experiment ($p_D = 0.45$ and $p_C = 0.5$).

Phase II sample size	Most probable state-decision at $t = 1$
30	(12,18) - No–Go
40	(15,25) - No–Go
50	(19,31) - No–Go
60	(23,37) - No–Go
70	(27,43) - No–Go
80	(31,49) - No–Go

Table 4.12: Most probable state and decision at $t = 1$ for the different Phase II sample sizes for the third experiment ($p_D = 0.45$ and $p_C = 0.5$).

4.1.1.4 Varying the Enrolment Cost

Another interesting experiment is to test the results we get when we vary the enrolment cost per patient. To do this, we use the same setup as in the first experiment (subsubsection 4.1.1.1), that is, we use the same parameters as Table 4.1. We also fixed the sample size to $k = 60$ (which was the optimal decision before). Contrary to before we use different costs per patient, $c \in \{4500, 5500, 6500, 7500, 8500, 9500, 10500, 11500\}$. We also note that to find the corresponding prior distribution values (s_0, f_0), we assume a sample size of 20 Phase I subjects and use the same seed (for consistency) in R to simulate them.

As expected, as we increase the cost per patient, we have an increasing number of "no–go" decisions, as we can see in Figure 4.4. The intuition behind this is that by increasing the cost of recruiting a patient, we increase the risk associated with potential large–scale Phase III trials.

Above, we argue how changing the cost per patient influences the decisions at $t = 1$. Perhaps a more interesting question is what happens at $t = 0$ (optimal Phase II sample size). To test this, using the same setup as before we tried the different costs on different Phase II sample sizes $k = \{30, 40, 50, 60, 70, 80\}$. The results can be seen in Figure 4.5. Interestingly, we see that higher costs per patient are linked to smaller Phase II sizes. This can be explained as the model optimises the revenue of a potential drug. Thus, having a smaller Phase II size,

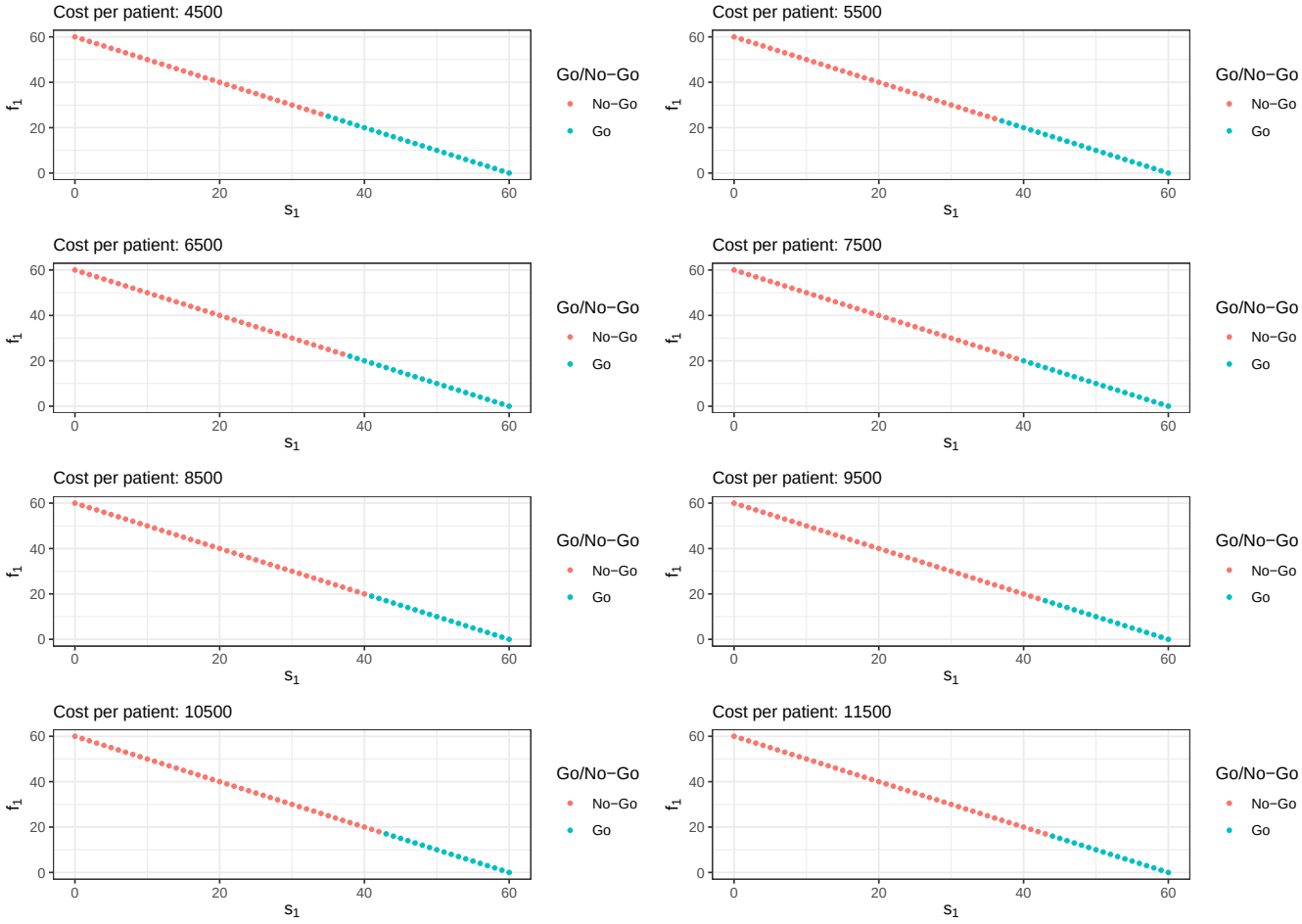

Figure 4.4: Optimal decisions ("go"/"no–go") for all combinations (s_1, f_1), for fixed Phase II size $k = 60$, using different cost per patient, for the fourth experiment ($p_D = 0.6$ and $p_C = 0.4$).

although might increase the risk of a false "no–go" decision for Phase III as we have a smaller sample, decreases overall costs and thus increases expected revenue.

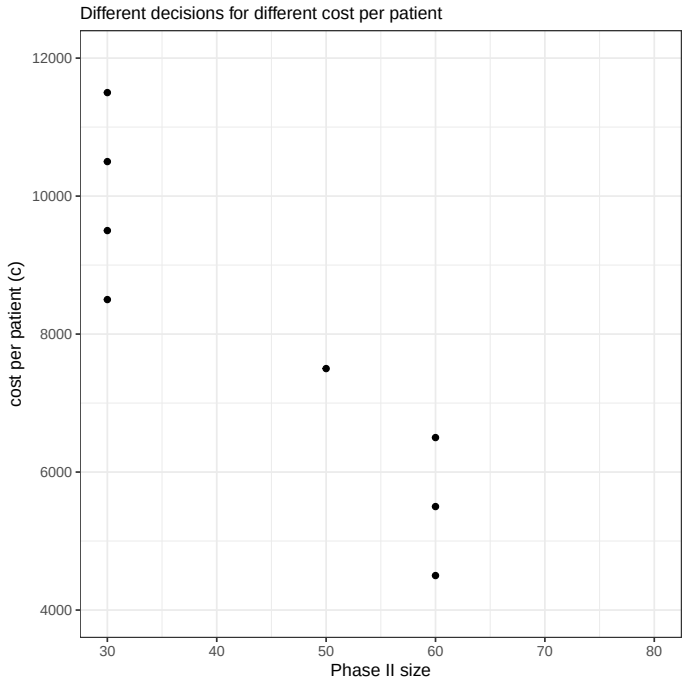

Figure 4.5: Optimal decision of Phase II sample size for different costs per patient, for the fourth experiment ($p_D = 0.6$ and $p_C = 0.4$).

Chapter 5

Conclusion

5.1 Summary

In this thesis we have investigated different clinical trial designs with their advantages and disadvantages, as well as a major challenge of the pharmaceutical sector, namely the fact that R&D productivity needs to be improved. This can be done in several ways; first, a straightforward method is to find creative ways to estimate the probability of approval (or probability of success) of the novel treatment. This provides a very useful insight to investors, as they can assess the risk and the expected net present value, thus allowing for a more informed decision.

The second approach is to use Machine Learning models to make data–driven decisions. Machine Learning methods, give useful information to investors and clinicians on certain factors that have some contribution (major or minor) in the drug's effectiveness and probability of approval. It is important to mention that these methods require access to clean data; otherwise, the results could be subject to bias.

Finally, a natural modelling possibility is the use of MDPs to find the most optimal decisions in the given environment. This framework allows the pharmaceutical company to adapt to different scenarios, e.g. rare diseases where due to their nature, we would, ideally, like to focus more on treating the patients currently enrolled in the clinical trial. Additionally, we believe that due to the post–COVID–19 era, where we start to move from the traditional RCTs, this type of modeling is going to be extensively used.

In the final part of the thesis we introduced a novel model with the aim of finding the optimal combination of Phase II–Phase III designs, which to the best of our knowledge has not been investigated before. We show that with, albeit limited testing, the model produces promising results, and it is definitely worth exploring further. Through a series of examples, we demonstrated how our model can be used in practice and we are confident that the extensions we aim to add are going to make it an attractive model in clinical decision–making.

5.2 Future Research Plans

In this section we give the ideas generated throughout the thesis but for lack of time and resources were not implemented. We address some of the limitations of our model and propose solutions to them. Our aim is to use these as a starting guide that would eventually lead to a more extensive research project.

5.2.1 Initial Goals

From experiments we ran with our model we are confident that it is a good model that can be used as a basis to build on. The most significant feature is the ability to identify a bad drug and correctly predict a "no–go" decision to Phase III.

5.2.1.1 Addressing Limitations

However, we believe that there is more experimenting to be done. Testing the model with different scenarios and different parameters, as well as including the potential of dropouts, will definitely give insight as to what can be improved. For example, something that needs to be addressed is the inability of our model to accurately identify novel treatments that are on the boundary of having clinically relevant treatment difference from the control.

We aim to solve this by using a more realistic way of defining the prior parameters (s_0, f_0). Instead of the prior parameters being dependent on just limited information from Phase I clinical data, we will assume (as is common), that clinicians have some level of optimism/pessimism (which will be based on pre–clinical testing) that the novel treatment will be successful. This information should and would be included in the prior parameters at Phase II by assuming the transition probability from $t = 0$ to $t = 1$ follows $G_0^a \sim Beta - binomial(T_a, s_0 + s_p, f_0 + f_p)$, for some s_p and f_p that fits the clinicians' knowledge.

A possible way to do this would be to give each of the clinicians working on the novel drug a survey regarding the treatment's effectiveness similar to what has been already proposed in (Hampson et al., 2022). This would give a crude approximation of the average effectiveness and certainty of the treatment. Then retrospectively, one could adjust the prior parameters mentioned above, to capture the clinicians' opinion.

In addition, something we mentioned in the text is the difficulty of quantifying the parameter C in practice. This parameter was added to give a penalty when we have a "no–go" decision and when we fail to reject the null hypothesis, as patients will not get access to a better treatment. We can think of this parameter as a way for a pharmaceutical company to balance maximising the potential revenue from a new treatment with the moral aspect of drug development. It is clear why this parameter is quite hard to quantify, and we could test how the model behaves if we completely remove it. Another solution would be to find a consistent way of quantifying it, without introducing any bias. A possibility would be to fix a percentage of the expected revenue and replace $C \cdot Pop$ (Equation 4.3a) and $C \cdot (Pop - n)$ (Equation 4.4) with it.

5.2.1.2 Adjust the Way We calculate the Phase III Sample Size

We also believe that we need to find a different way of calculating the Phase III sample size (Equation 4.2). Let's imagine a scenario where the Phase II proportion of successes for treatment D is "close" to the proportion of successes for treatment C. Then, the idea is that we would probably require a larger sample size to identify a clinically relevant difference (if it exists), but not too large as that would return statistically significant results even for very

small differences between the treatments. On the other hand, if the two treatment success proportions are "far" from each other, then a bigger trial would be wasteful.

Our idea is to use a Bayesian sample size calculation which actually uses Equations 3.1, 3.2 (Kunzmann et al., 2021). This Bayesian viewpoint on sample size derivation for frequentist trials could probably balance the claims we made above by taking into account alternative plausible treatment effects via a prior distribution. This framework would also fit naturally in the clinical trial context as normally clinicians working on the drug have some optimism/pessimism about the novel drug.

5.2.2 Longer Term Goals

In this subsection we give our long term goals for this research project. We provide extensions to the starting model that are required since our aim is to provide a fully–developed tool that can be used by decision makers in practice.

5.2.2.1 Consider Multiple Outcomes

As of now, the model only considers limited options. More specifically it considers efficacy outcomes on one binary endpoint, which means that we only focus on meeting statistical significance on one key endpoint. The next step would be to start considering different endpoints (time–to–event) and more than one efficacy endpoints. Additionally, following (Hampson et al., 2022), we also aim to include safety outcomes, since the ultimate goal is to make this model a tool that can be effectively used in practice.

5.2.2.2 Decision on Joining a Platform Trial

A more complicated model would be the following. Instead of having a choice at $t = 0$ between the K different sample sizes, the two competing options would be to either join an existing platform trial or set up a company's own trial (either one–armed or two–armed). By joining the platform trial, patients would be allocated to the treatment according to that trial's rules. On the other hand, if the company runs its own trial, then each patient will have the choice of either entering the existing platform trial, or joining the company's trial. A (reasonable) assumption we can make here is that patients would act rationally and choose to join the trial that would give them a higher chance of getting a better outcome. This would make the mathematical model more straightforward.

5.2.2.3 Include Interim Analyses Points

We have previously mentioned that companies may assess the quality of treatments during intermediate stages of clinical trials in order to find inferior drugs early and stop their development. These interim analyses (IA) points have gained popularity in clinical trials over the past three decades as a means of lowering expenses as well as a means of assisting businesses in making quicker choices and stopping clinical studies when necessary. Therefore it is only logical we include these IAs in our model.

To incorporate these points in our model, we could use accumulated data after each IA to update the transition probability distribution. We assume a fixed number of IAs, say $l = 1, \ldots, L-1$, which happen at times $\tau_1, \ldots, \tau_{L-1}$, and the final analysis occurs at time τ_L. Having said that, we, will slightly abuse the notation from the original model and, split the time from $t = 0$ to $t = 1$, to $\tau_0 = 0, \tau_1, \tau_2, \ldots, \tau_{L-1}, \tau_L = 1$. We also assume that at each interim analysis point τ_l we update our belief using responses gathered from n_l patients and denote s_l (f_l) the number of successes (failures) observed during the period from τ_{l-1} to τ_l. Then the transition probability from τ_{l-1} to τ_l will be given by using the cumulative successes and failures until τ_{l-1} via $G_{\tau_{l-1}} \sim Beta - binomial(T_j, s_0 + \sum_{i=1}^{l-1} s_i, f_0 + \sum_{i=0}^{l-1} f_i)$.

Using this procedure will allow us to incorporate data from IA points and utilise them within our model, which will eventually lead to more accurate results. The rest of the model (from $t = 1$ to $t = 2$) would stay the same, unless we also want to include IA points in the Phase III trial, in which case we would use the same procedure.

5.2.2.4 Focus on Lung Cancer Trials

The ultimate goal of this research project is to help in decision–making relevant to lung cancer studies, more specifically to find whether it is optimal to participate in a platform trial or for the firm to conduct its own custom trial. In this thesis we focused on binary outcome data which is not realistic as typically Phase III lung cancer trials involve time–to–event outcome such as overall survival, progression–free or event–free survival as the primary efficacy endpoint (Ananthakrishnan et al., 2021). Thus, it is crucial to find clever ways to cope with this.

A possible way to model this would be to assume the proportional hazard condition, which is common in practice (Ananthakrishnan et al., 2021), and use the Cox proportional hazards model (Cox, 1972), which assumes the hazard function is written as follows,

$$h(t) = h_0(t) \cdot \exp\{\beta_1 x_1 + \cdots + \beta_p x_p\},$$

where $x_1, \ldots, x_p$ are covariates, that could include certain disease–specific measures, such as tumor size at the time of measurement or be more patient–centric and include variables such as biomarker status of the specific patient.

The way to incorporate this into our MDP model would be to include the covariates in the state vector and at every decision epoch estimate the parameters β using the partial likelihood function (Cox, 1972),

$$PL(\beta) = \prod_{i=1}^{n} \left\{ \frac{\exp(\beta^T x_i)}{\sum_{j \in R_i} \exp(\beta^T x_j)} \right\}^{\delta_i},$$

and choose the action that minimises the hazard function, as this implicitly suggests that the chosen action maximises the benefit for the patient.

We note here that the details for the proposed method, such as the time epochs, transition probabilities, reward function etc., need to be clearly formulated to see whether this idea can be used in practice. The main limitation that would need to be solved is the computational complexity, for which we could use methods from approximate dynamic programming.

Another possible direction would be to choose a test statistic commonly used for the survival model, at Phase III say. Then, we would create the state vector by making a discrete approximation to the feasible values of the test statistic and use the MDP framework to find the optimal actions. Again, details of the method would need to be clearly formulated to identify potential issues.

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