

# DOCTORAL THESIS

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## **Developments to established dose-finding methodologies for application in trials with complex and innovative designs**

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# *Abstract*

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by Amit PATEL

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## **Chapter 1**

### **Introduction**



## Chapter 2

# Implementing the PO-TITE-CRM trial design into ADePT-DDR

### 2.1 Introduction

Worldwide there are approximately 600,000 new cases of Head and Neck Squamous Cell Carcinoma (HNSCC) each year [1]. Of which, 12,000 occur in the UK with the most common forms of treatment being surgery, radiotherapy and/or chemotherapy [2]. Radiotherapy is essential for the treatment of cancer. It has been estimated that more than 40% of patients will receive radiotherapy at some point in their treatment [3]. However, despite recent advancements in radiation techniques and the use of concomitant chemoradiotherapy, patients with solid tumours such as head and neck cancer have suboptimal cure rates [2], [4]. For those with advanced HNSCC primary radiotherapy with concurrent chemotherapy is often offered but, it has not been shown to improve survival in patients aged over 70 compared to radiotherapy alone [5]. Therefore, any strategy to improve the efficacy of radiotherapy without increasing toxicity would have a significant impact on patient outcomes.

DNA damage repair (DDR) inhibition is a potential technique which could

be utilised as it potentiates the therapeutic effects of ionising radiation in cancer cells [6]. Combining radiotherapy with DDR inhibition could improve clinical outcomes for these patients [7].

The ADePT-DDR trial<sup>1</sup> is a platform trial which aims to evaluate the safety and efficacy of different DDR agents, or different immunotherapy agents and/or DDR and immunotherapy combinations, together with radiotherapy in patients with HNSCC. The initial component of this trial is a single-arm dose-finding trial investigating the ataxia telangiectasis and Rad3-related (ATR) inhibitor AZD6738 in combination with radiotherapy. ATR inhibitors not only stop DNA repair but impair the mechanism that allows for repairs to take place. Preclinical models have shown this double blocking to be effective in killing cancer cells [8].

Traditionally dose-finding trials aim to determine the maximum tolerated dose (MTD) of a treatment based on the cytotoxic assumption that the most toxic dose is the most efficacious. Rule-based or 'up and down' designs achieve this by escalating and de-escalating doses dependent on the observation of severe toxicity due to the drug, commonly referred to as a dose-limiting toxicity (DLT). In the case of the 3+3 design, escalation continues until at least two patients in a cohort of three or six experience a DLT. More explicitly, the MTD is the dose level below the dose at which  $\geq 33\%$  of patients experience a DLT [9]. Model-based designs such as the continual reassessment method (CRM) [10] work on the assumption that the probability of toxicity increases monotonically with increases in dose levels. The CRM aims to find the MTD which is a dose with specified target toxicity level.

Due to the historical use of rule-based designs [11], [12], the majority of the terminology used to describe them, and the ambiguity they raise, have been

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<sup>1</sup>Accelerating the Development and implementation of Personalised Treatments of DNA Damage Response agents and radiotherapy +/- immunotherapy for head and neck squamous cell cancer



inherited by modern designs such as the CRM. The MTD in the context of a CRM is not the 'maximum' dose patients could tolerate but rather a dose in which there would be an acceptable target probability of a DLT occurring. For example, if the target is set at 25% the MTD would be the dose at which there is a 25% probability of experiencing a DLT. Rather than using the term MTD, the dose to be found will be referred to as the target dose (TD%%, where the %'s are replaced by the target probability), i.e. TD25 would be the dose expected to be toxic in 25% of patients.

The investigation of multiple-agent treatments, where the monotonicity assumption may not hold, is increasing in early phase trials. Finding the TD in combinations of treatments, compared to single-agents, presents methodological challenges. Each drug individually may obey the monotonicity assumption we can refer to this as the doses being fully ordered. However, when multiple treatments are combined, the ordering of doses in terms of toxicity may not be fully apparent or may only be partially ordered. An order may be identified for a subset of the doses which would result in a partial order. Without a fully understood ordering it is uncertain which dose should be chosen in decisions of escalation and de-escalation and ultimately as the TD. This issue is not exclusively reserved for trials with multiple-agents. The monotonicity assumption may not hold for certain drugs in single-agent studies leading to partial orders of dose toxicity. For example, when dose and frequency of administration vary between dose levels. Monotonicity is a very strong assumption. It requires that probability of toxicity always increases - staying the same is not enough. At high enough doses, this assumption is almost surely violated for all interventions when the event probability reaches its maximum. Thus, even when total ordering is possible, the monotonicity assumption could be violated [13]. This can occur in scenarios where multiple parameters of the treatment schedule

are altered for each dose level. For example, either dose or treatment duration could be increased and even if patients receive an equal dose it would remain unclear as to if prolonged exposure to a lower dose is more toxic than short exposure to a higher dose, which implies a partial ordering of toxicity probabilities.

Further methodological challenges revolve around the issue of late-onset toxicities. Typically, early phase trials implement a short window to observe DLTs. This works well in situations where toxicities are likely to occur rapidly after treatment. However, this is not optimal for treatments that could cause late-onset toxicities such as radiotherapy. The aim with ADePT-DDR would be to incorporate a larger observation window to account for potential late-onset toxicities whilst also minimising the trial duration.

Cheung and Chappel [14] introduced an extension to the CRM to deal with the issues of treatments that may cause late-onset toxicity. This design referred to as the time-to-event CRM (TITE-CRM), uses a weighted dose-response model to incorporate the time it takes for a DLT to occur in a patient. There have also been published trial designs to deal with the issues that arise from investigating combinations of treatments. Thall et al. [15] proposed an adaptive two-stage Bayesian design which utilises a parametric model of toxicity as a function of two doses. Yin and Yuan [16] present a Bayesian design that uses a copula regression model to evaluate the joint toxicity probabilities of combined drugs. The continual reassessment method for partial orders (PO-CRM) developed by Wages et al. [17] extends the CRM design by relaxing the assumption of monotonicity and by modelling different potential orders. Figure 2.1 shows a simple example of partial ordering where the order of two out of the four dose levels are unknown.

Wages et al. [17], [18] further developed their work on the PO-CRM to deal with late-onset toxicities by implementing a TITE component. This trial

FIGURE 2.1: Example dose levels to illustrate partial ordering.



design, referred to as the time-to-event continual reassessment method in the presence of partial orders (PO-TITE-CRM) by the authors, was chosen to be used in ADePT-DDR. A search of PubMed, conducted on the 25th of July 2020, found six articles that had cited the PO-TITE-CRM design by Wages et al. [18]. Of these six articles non actually implement the design into a trial. The following paragraphs provide more details.

Five of these papers were methodological in nature, two of which only include the PO-TITE-CRM design in a brief introduction to current methodology before going on to present new Bayesian trial designs [19], [20]. The other three papers were authored by Wages. The first of which details practical considerations and specifications for the PO-CRM design, the TITE variant is only cited as the source of an example which is being used [21]. One paper presents an R package ‘pocrm’ [22], [23]. The package is only capable of analysing the PO-CRM design. The TITE variant is only referenced here as it illustrates the issue

of partial ordering. The last methodological paper by Wages et al. [24] presents three different methods for phase I studies of drug combinations one of which is the PO-CRM however, PO-TITE-CRM is only mentioned as an extension to this design. A key message in this paper is the fact that novel methodologies are constantly emerging but are rarely implemented in practice.

The last paper is a protocol paper for a phase I/II study, OLA-TMZ-RTE-01 [25]. The phase I component of the study aims to determine the recommended phase II dose (RP2D) of olaparib combined with a standard schedule of radiotherapy and temozolomide (TMZ) as first line treatment for patients with unresectable glioblastoma (GBM). The treatment schedule is divided into a radiotherapy and maintenance period. They propose to conduct two sequential dose-escalations of seven different olaparib dose-levels. Patients in the first escalation will be allocated to a dose level of olaparib for 10 weeks including radiotherapy for six weeks with TMZ given each day during radiotherapy and then for six cycles four weeks post radiotherapy during the maintenance period. They state the MTD1 will be determined using a TITE-CRM. Patients in the second escalation olaparib at the MTD1 during the radiotherapy period along with the same schedule of radiotherapy and TMZ. Those patients will then be allocated to one of the seven dose levels of olaparib during the maintenance period. Again, it is stated that the MTD2 will be determined using TITE-CRM modelling. The RP2D is the MTD1 and MTD2 during the radiotherapy and maintenance period respectively. Even though a combination of treatments is being investigated only olaparib is being escalated and doses for other treatments are fixed for all patients. Furthermore, the dose-levels for olaparib increase consistently in either amount or duration meaning there are no issues of partial ordering which would warrant the use of PO-TITE-CRM. The authors reference the TITE-CRM methodology with two papers. One of them

being the paper detailing the PO-TITE-CRM design and the other being a paper by Huang and Kuan [26] which proposes an adaptive weight function that incorporates cyclical data of treatment into the TITE-CRM. It is unclear as to why the PO-TITE-CRM is cited as its methodology is not mentioned anywhere in methods.

This is just a brief review of the current literature but it seems that the PO-TITE-CRM has rarely been used or discussed since its inception.

This chapter provides novel insight into the methodology of PO-TITE-CRM through application in a real-world scenario. Section 2.2 will detail how the PO-TITE-CRM works. Section 2.3 discusses the justification for implementing the design into the ADePT-DDR trial and our experiences doing so. Section 2.4 explores other alternative designs which could have been implemented and assess how they perform in comparison to the PO-TITE-CRM. We provide some discussion in Section 2.5 and finally some conclusions in Section 2.6.

## 2.2 The PO-TITE-CRM Design

Wages et al. [18] introduced the PO-TITE-CRM design which builds directly upon the PO-CRM design by incorporating a TITE component into the dose toxicity model. The aim of which is to determine the target dose for combinations of drugs where the monotonicity assumption does not hold, in a setting where late-onset toxicities are possible.

TABLE 2.1: Example of drug combinations for a trial investigating two agents.

<b>Agent</b>	<b>Drug combinations</b>					
	$d_1$	$d_2$	$d_3$	$d_4$	$d_5$	$d_6$
A (mg/day)	0.25	0.5	1.0	0.25	0.5	1.0
B (mg/day)	1.0	1.0	1.0	1.5	1.5	1.5

To help understand partial ordering, consider an example of an early phase trial investigating the combination of two agents. Drug A which consists of three doses (0.25, 0.5, 1.0 mg/day) and drug B which consists of two doses (1.0, 1.5 mg/day), for a total of six drug combinations  $d_1, \dots, d_6$  (Table 2.1). For each drug independently we assume they have a monotonic dose-toxicity curve however, the ordering of toxicity probabilities for some of the treatment combinations is unknown. Specifically, we can say  $d_1$  is less toxic than  $d_2$  as the dose of drug A increased whilst the dose of drug B stayed the same. This is also the case for  $d_2$  and  $d_3$ . So,  $d_1$  can always be considered less toxic than  $d_2$  which is always less toxic than  $d_3$ . The same can be said for doses  $d_4, d_5$  and  $d_6$ , these three doses are can also all be considered more toxic than  $d_1$  as well. The order between  $d_4$  and  $d_5$  in comparison to  $d_3$  is not known because the dose of drug A decreases whilst the dose of drug B increases. Similarly the order between  $d_2$  and  $d_4$  is unknown. Also, we can say that  $d_6$  is the always the most toxic dose. Assessing all these potential order toxicity relationships leaves five possible orderings.

1.  $d_1 \rightarrow d_2 \rightarrow d_3 \rightarrow d_4 \rightarrow d_5 \rightarrow d_6$
2.  $d_1 \rightarrow d_2 \rightarrow d_4 \rightarrow d_3 \rightarrow d_5 \rightarrow d_6$
3.  $d_1 \rightarrow d_2 \rightarrow d_4 \rightarrow d_5 \rightarrow d_3 \rightarrow d_6$
4.  $d_1 \rightarrow d_4 \rightarrow d_2 \rightarrow d_3 \rightarrow d_5 \rightarrow d_6$
5.  $d_1 \rightarrow d_4 \rightarrow d_2 \rightarrow d_5 \rightarrow d_3 \rightarrow d_6$

Using the notation of Wages et al. [17], [18], let  $M$  denote the number of possible orders and  $Y$  be an indicator of a toxicity event. Then for a trial investigating  $k$  combinations,  $d_1, \dots, d_k$ , the dose for the  $j$ th patient,  $X_j, j = 1, \dots, n$  can be thought of as random  $x_j \in (d_1, \dots, d_k)$ . For a specific ordering  $m, m = 1, \dots, M$

the toxicity probability  $R(d_i)$  is modelled by

$$R(d_i) = \phi_m(d_i, w, \beta) = w\psi_m(d_i, \beta) \quad i = 1, \dots, k; \quad m = 1, \dots, M \quad (2.1)$$

for a weighted dose response model  $\phi_m(d_i, w, \beta)$  where  $\beta \in (-\infty, \infty)$ . The weight,  $w$  as defined by Cheung and Chappel [14], is a function of the time-to-event of each patient and is incorporated linearly with the dose toxicity model  $\psi$  so that  $0 \leq w \leq 1$ . Each patient is followed for a fixed amount of time  $T$ . Let  $U_j$  represent the time-to-toxicity of patient  $j$ . Then for  $u \leq T$ ,

$$P(U_j \leq u) = P(U_j \leq u | U_j \leq T)P(U_j \leq T) \equiv w(u; T)\psi_m(d_i, \beta). \quad (2.2)$$

For simplicity we will refer to the weight function  $w(u; T)$  as  $w$ . The weight function will have to be decided upon by the trials team, dependent on the scenario, a simple linear function or a more complex adaptive weights function could be utilised. There are also several working dose models which could be used for  $\psi$ , Wages et al. [18] present their design with the power parameter model given by

$$\psi_m(d_i, \beta) = \alpha_{mi}^{\exp(\beta)} \quad i = 1, \dots, k; \quad m = 1, \dots, M. \quad (2.3)$$

Here  $0 < \alpha_{m1} < \dots < \alpha_{mk} < 1$  are the prior estimates of toxicity probabilities, or skeleton, for each potential ordering. Furthermore, prior probabilities are assigned to each order  $M$  to account for any prior information regarding the plausibility of each model such that,  $p(m) = \{p(1), \dots, p(M)\}$ , where  $p(m) \geq 0$  and  $\sum_m p(m) = 1$ . When all orders are equally likely or there is no prior information available on possible orderings the prior is discretely uniform and would be  $p(m) = 1/M$ .

A Bayesian framework is used and a prior probability distribution  $g(\beta)$  is

assigned to the parameter  $\beta$ . The ordering with the largest prior probability is selected as the starting ordering, in the scenario where all priors are equal an ordering is selected at random, subsequently a starting dose is also chosen. After  $j$  patients have been entered into the trial data is collected in the form of  $\Omega_j = \{x_1, y_1, \dots, x_j, y_j\}$ . A weighted likelihood for the parameter  $\beta$  is used to establish running probabilities of toxicity for each treatment combination. The weighted likelihood under ordering  $m$ , is given by

$$\tilde{L}_m(\beta|\Omega_j) = \prod_{l=1}^j \phi_m^{y_l}(x_l, w_l, \beta) \{1 - \phi_m(x_l, w_l, \beta)\}^{(1-y_l)} \quad (2.4)$$

which can be used to generate a summary value  $\hat{\beta}_{mj}$  for each ordering. With the likelihood and the data  $\Omega_j$ , the posterior density for  $\beta$  can be calculated using

$$\tilde{f}_m(\beta|\Omega_j) = \frac{\tilde{L}_m(\beta|\Omega_j)g(\beta)}{\int_{\beta} \tilde{L}_m(\beta|\Omega_j)g(\beta)d\beta} \quad (2.5)$$

This can then be used to establish posterior probabilities of the orderings given the data as

$$\tilde{\pi}(m|\Omega_j) = \frac{p(m) \int_{\beta} \tilde{L}_m(\beta|\Omega_j)g(\beta)d\beta}{\sum_{m=1}^M p(m) \int_{\beta} \tilde{L}_m(\beta|\Omega_j)g(\beta)d\beta}. \quad (2.6)$$

We select the single ordering,  $h$ , with the largest posterior probability along with its associated working model  $\psi_h(d_i, \beta)$  and generate toxicity probabilities for each dose level. Once the  $j$ th patient has been included the posterior probability of DLT can be calculated for  $d_i$  so that

$$\hat{R}(d_i) = \psi_h(d_i, \hat{\beta}_{hj}); \hat{\beta}_h = \int_{\beta} \beta \tilde{f}_h(\beta|\Omega_j)d\beta. \quad (2.7)$$



In turn, the dose level  $x_j \in \{d_1, \dots, d_k\}$  assigned to the  $(j+1)$ th patient is the dose,  $d_i$ , which minimises

$$\Delta(\hat{R}(d_i), \theta) = |\hat{R}(d_i) - \theta|, \quad i = 1, \dots, k \quad (2.8)$$

where  $\theta$  is the target toxicity rate. Similarly, once all patients have been recruited and observed and the trial ends, the target dose ( $TD_\theta$ ) is the dose,  $d_i$ , which minimises (2.8).

## 2.3 PO-TITE-CRM in ADePT-DDR

The decision to implement PO-TITE-CRM into ADePT-DDR was made by Piers Gaunt (PG) after discussions with other statisticians Kristian Brock (KB) and Daniel Slade (DS), as well as the chief investigator and other co-investigators. The design was chosen as the toxicity probabilities of the dose levels weren't monotonically increasing which restricts the use of most early phase designs such as the CRM. Additionally, the design also handles late-onset toxicities which would be an issue in ADePT-DDR due to the treatment involving radiotherapy. The availability of software to conduct the trial was also a factor that was considered. The R package 'pocrm' [22] only provides a means for implementing the PO-CRM design but the easy accessibility to this code meant that it could be extended to include the TITE component.

The intended use of this design is for dose-finding in combinations of therapies, as this is the source of the partial ordering issue. ADePT-DDR however, is a unique implementation of the design as even though it involves a combination of therapies (radiotherapy and AZD6783) the dose of radiotherapy is fixed and dose-finding is only planned for AZD6783. PO-TITE-CRM is still applicable in this case as the design includes combinations of dose and duration

for AZD6783 which are partially ordered.

A two-stage PO-TITE-CRM will be used to find the TD25 of AZD6783. This will be determined by dose-limiting toxicities evaluated by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and Radiation Therapy Oncology Group (RTOG) late toxicity score. The binary DLT events are pre-defined by a variety of grade 3-4 adverse events notably, haematological, cardiovascular and gastrointestinal/hepatic toxicities as well as significant non-haematological events and specific treatment-related toxicities. DLTs will be monitored for the duration of treatment (seven weeks) and throughout the follow-up period. The total follow-up period post treatment is 52 weeks, so patients will spend a total of 59 weeks in the trial.

A maximum of 60 patients will be recruited for the dose-finding aspect of this trial and up to 20 patients as controls. Controls will be utilised to make comparisons for secondary outcomes such as survival and efficacy. Control patients will only be receiving radiotherapy, the dose of which is fixed at 70Gy/35F. Cohorts of three patients will be recruited and assigned to dose levels chosen by the PO-TITE-CRM. Controls will be recruited in the interim period between the recruitment of the third patient in a cohort and the completion of the minimum follow-up period.

### **2.3.1 Partial Ordering in Practice**

Each patient entered into ADePT-DDR will receive fixed dose radiation, totalling 70 Gy in 35 fractions over seven weeks. For the dose-finding aspect we investigate six doses of AZD6783 detailed in table 2.2. Treatment dose and duration to be selected for dose level 3 will be determined based on a combination of data observed, adverse events and compliance. The issue of partial ordering is illustrated in Figure 2.2 inspired from plots by Wages et al. [18]. The doses

to be used in this trial are detailed in their appropriate box. Additionally, each dot represents a potential dose combination which theoretically could be investigated. The combinations are colour coordinated to indicate where partial ordering exists in this dose combination space. Doses across the same colour (each diagonal) cannot be distinguished from each other in terms of probability of toxicity. However, it forms a hierarchy in which doses of the same colour can be thought of as less/more toxic than doses in another colour i.e the red dose levels would have a higher probability of toxicity than the yellow dose levels. It is clear that dose levels 2a and 2b would be considered more toxic than dose level 1 due to the increase in treatment duration and treatment dose respectively. When comparing 2a and 2b it is unknown whether the increase in dose or duration will be more toxic. Hence there are two possible orderings for ADePT-DDR.

$$1. d_{-1} \rightarrow d_0 \rightarrow d_1 \rightarrow d_{2a} \rightarrow d_{2b} \rightarrow d_3$$

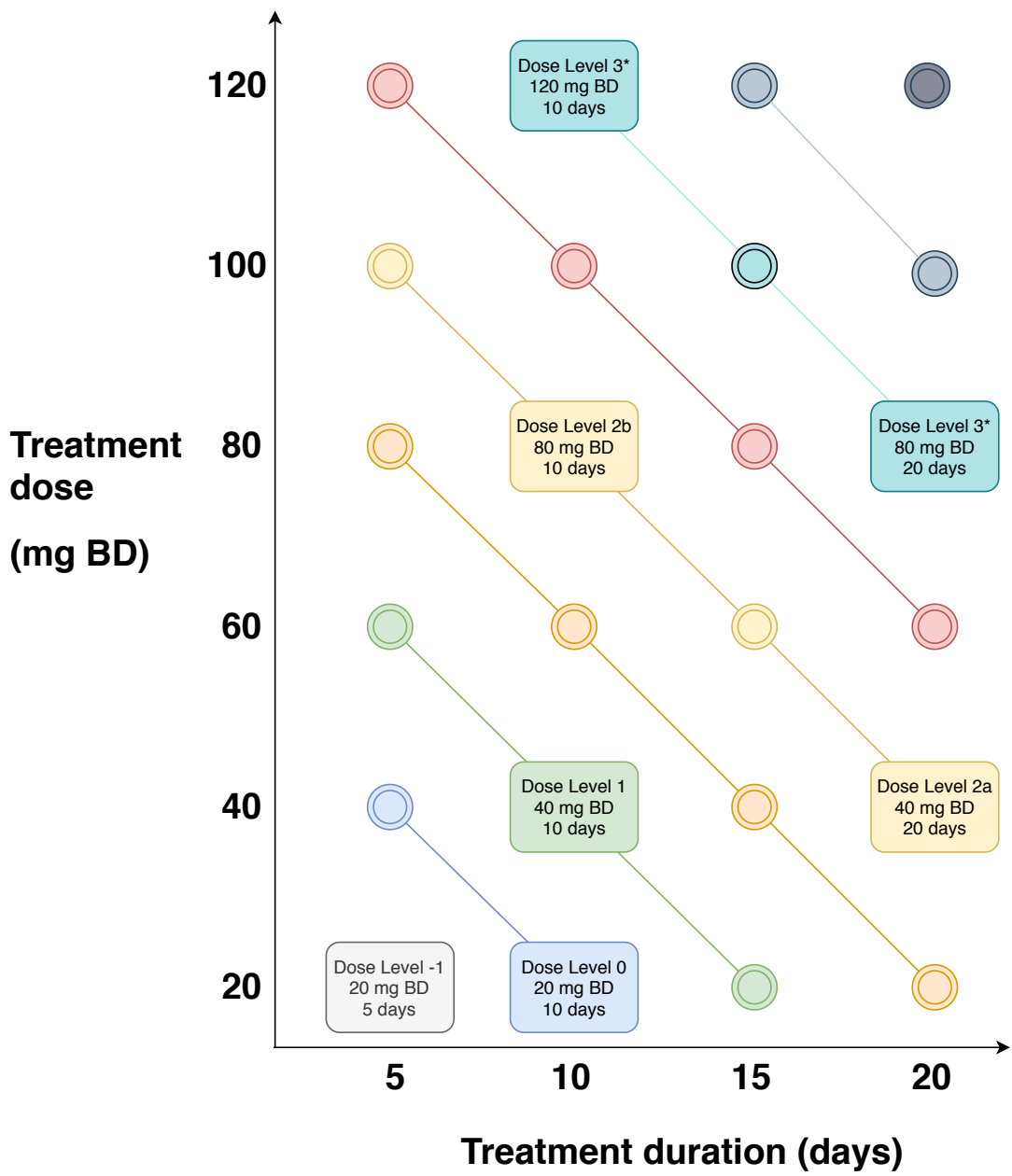
$$2. d_{-1} \rightarrow d_0 \rightarrow d_1 \rightarrow d_{2b} \rightarrow d_{2a} \rightarrow d_3$$

TABLE 2.2: ADePT-DDR dose-levels and duration of treatment for AZD6783.

Dose Level	AZD6783 Daily dose (mg BD)	Weeks	Duration (days)	Radiotherapy
-1	20	1	5	70 Gy/ 35 F
0	20	1&4	10	70 Gy/ 35 F
1	40	1&4	10	70 Gy/ 35 F
2a	40	1,2,4&5	20	70 Gy/ 35 F
2b	80	1&4	10	70 Gy/ 35 F
3	120	1&4	10	70 Gy/ 35 F
	80	1,2,4&5	20	70 Gy/ 35 F

Traditionally, dose-finding trials for combinations would select dose levels to form a 'path' through the dose combination space such that each subsequent dose level was logically more toxic. This avoids the issue of partial ordering

FIGURE 2.2: ADePT-DDR dose levels across dose and duration.



but means doses of interest or effective dose combinations may be missed or not investigated. Specifically, for ADePT-DDR this allows two 'paths' from dose level 1 extending to 2a and 2b. In terms of dose level 3 only one of the doses in that tier will be investigated, it was unclear as to which dose level would be best due to a lack of historical data. Even though dose level 3 is not yet specified in terms of modelling and simulations it was treated as singular

dose. This was done as clinicians thought that it would be unlikely that we'd reach these doses and that the probability of toxicity between them would be similar.

Preliminary designs of the trial included only five dose levels and planned to use dose level 0 as the starting dose. During the trial design phase it was decided a new lower dose (dose level -1) would be introduced to allow for de-escalation if the initial dose was found to be too toxic. Dose escalation/de-escalation for subsequent cohorts would be determined from the two-stage PO-TITE-CRM. A two-stage design allows for escalation according to a pre-defined escalation scheme similar to a '3+3' design. The first stage dictates that if no DLT's are observed in the current cohort the dose allocated to the next cohort is the following dose in the escalation scheme. Dose levels continue to be incremented in this fashion until the first DLT is observed. In stage two, dose levels are determined by the PO-TITE-CRM.

Typically CRM designs begin by testing the first patient, or cohort, at the prior guess of TD or at a lower dose to be safe. However, clinicians may have safety concerns beginning the trial at higher dose levels as well as escalating to higher dose levels without testing lower ones. Investigators in ADePT-DDR expressed similar concerns as such a two-stage design was adopted. The escalation scheme used in stage one of ADePT-DDR will follow that of the first ordering ( $d_{-1} \rightarrow d_0 \rightarrow d_1 \rightarrow d_{2a} \rightarrow d_{2b} \rightarrow d_3$ ). If patients in the first cohort (assigned to dose level 0) don't experience a DLT the next cohort will be allocated to dose level 1 and then if no DLTs are observed again the third cohort will be allocated to dose level 2a and so on and so forth. The dose escalation scheme was determined based on the prior probabilities of toxicity generated for each dose level.

Information elicited from the investigators helped generate prior probabilities of toxicity for each dose level. They believed that dose level 2b would

be the TD25 with 2a being less toxic. This was used in conjunction with the `getprior` function from the `dfcrm` R package [27] which yielded priors of 0.012, 0.036, 0.084, 0.157, 0.25 and 0.355 for dose levels -1, 0, 1, 2a, 2b and 3 respectively. The half-width of the indifference interval was set at 0.05. The indifference interval is an interval in which the toxicity probability of the selected dose will eventually fall. Prior probabilities are also required for the plausibility of each model and even though the clinicians think that 2b will be more toxic than 2a there is no clear evidence and still a lot of uncertainty. As such it is sensible to assume a plausibility probability of 0.5 for each ordering, implying both orders are equally likely to be the true ordering of these dose levels.

### 2.3.2 The TITE component

The observation window for this trial will be up to a year post-treatment as the combination of radiotherapy with AZD6738 is anticipated to cause late-onset toxicity. The Acute DLT observation period is 12 weeks (84 days) post radiotherapy end with a minimum of 8 weeks (56 days) for the last patient of each cohort. However, patients will continuously be monitored for occurrence of DLT for at least 12 weeks (84 days), i.e. at least 12 weeks (84 days) from the end of radiotherapy. The full window will last for 52 weeks (365 days) post-treatment.

The TITE component incorporates a weighting contribution for each patient dependent on how long that patient has been evaluable in the study. This allows a patient to be evaluated once they have been observed for the minimum DLT period of 8 weeks (56 days). The weighting at this point is 60% rising to 80% at 12 weeks (84 days). A patient will not contribute fully to the model until they have completed 52 weeks (365 days) follow up (or have experienced a DLT at any stage in which case they will be weighted as a whole

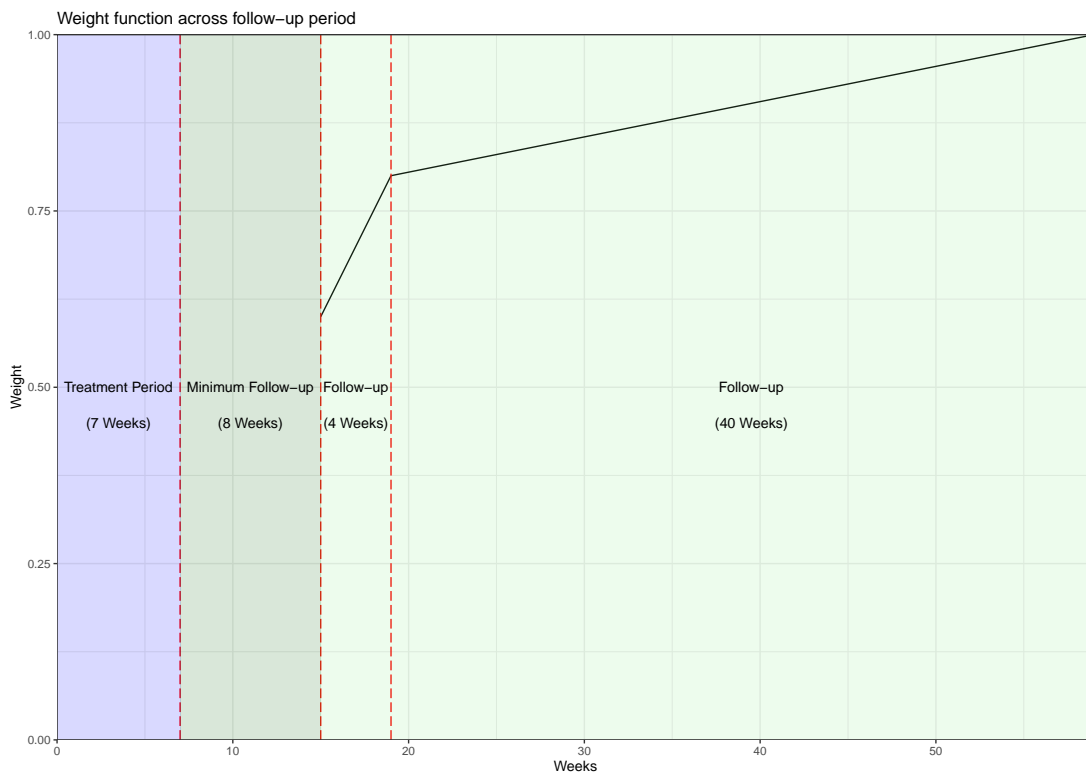
contribution). Linear weighting functions will be employed for any patient with a length of follow up between these three time points. One weight function to calculate weights between 8-12 weeks and another for weights between 12-52 weeks. For the weighting function  $w(u; t_1, t_2, t_3)$  where  $u$  is the time-to-toxicity of patient  $j$  and  $t_1, t_2, t_3$  is the time time period with values 8, 12 and 52 respectively. Then for  $t_1 \leq u \leq t_3$

$$w(u; t_1, t_2, t_3) = 0.6 + 0.2 \frac{\min(0, \min(u, t_2) - t_1)}{t_2 - t_1} + 0.2 \frac{\max(0, u - t_2)}{t_3 - t_2}. \quad (2.9)$$

All patients will have a minimum weight of 60% as that is the prescribed weighting to the minimum follow up period before dose escalation/de-escalation decisions can be made. For each additional week the patient is observed, without a DLT occurring, between weeks 8 and 12 their weighting increases by 5%. Similarly for each week between 12 and 52 weeks, without a DLT, weighting increases by 0.5%. Figure 2.3 illustrates the weight function and how the weight changes for patients dependent on how long they have been followed-up.

The TITE-CRM originally presented by Cheung and Chappel [14] did not incorporate a minimum follow-up period and their design allowed for the continual recruitment of patients whenever they became available. There are some practical considerations which make this infeasible in ADePT-DDR. The model would need to be run each time a new patient entered the study which requires statistical input hence the introduction of cohorts. Clinicians may also have safety concerns if we see rapid recruitment at the start of the trial and the model keeps escalating so we impose a minimum follow-up period. Initially this was set at 12 weeks (at 80% weighting) however, statisticians AP and PG pointed out that dose escalation/de-escalation decisions would have to take place 19 weeks (7 weeks treatment and 12 weeks follow-up) after recruitment

FIGURE 2.3: Weights of patients who have not experienced a DLT across the observation window.



of the third patient in the cohort. Dependent on the recruitment rates this could extend the duration of the trial and negates the benefits of using a TITE design. The investigators also agreed this was too long and settled on lowering this period to 8 weeks (at 60% weighting) whilst also including the original 12 week weighting of 80%.

### 2.3.3 Stopping Rules

A practical modification was included to allow for early stopping of the trial if there is sufficient evidence that the TD has been reached. Sufficient evidence is achieved once 15 patients (five cohorts) have been treated at the same dose level and the model allocates that dose level again to a sixth cohort. This rule evolved from the original designs of the trial which involved 30 patients with a dose expansion cohort to ensure at least 15 patients were treated at the TD.



Initial simulations highlighted the inadequacy of these design parameters as operating characteristics for various scenarios were poor, specifically in terms of correct TD selection. Clinicians explained the inclusion of the dose expansion cohort was to ensure the dose-finding aspect of the trial did not take a large amount of time whilst also allowing safety to be assessed at the TD. In order to ensure that a reasonable amount of patients would be treated at the TD, the trial wouldn't take longer than necessary and operating characteristics improved, the sample size was increase and this rule was introduced.

A rule was also implemented to allow for early termination of the trial in the case of excess toxicity at the lowest dose. If the probability of DLT at the lowest dose is higher than 0.35 with a probability of 80% and has been tested the trials safety committee will be alerted and will recommend if the trial should be stopped. As the trial starts at dose level 0, which is not the lowest dose, it is possible for the trial to recommend terminating without ever allocating patients to the lowest dose level. As such it was decided early termination would only occur once at least 3 patients (1 cohort) have been allocated dose level -1.

An approximate estimate of the variance was calculated using methodology presented by O'Quigley and Shen [28]. The observed information matrix is obtained by taking the second derivative of the likelihood (eq. 2.4) which is then used to calculate the variance  $v(\hat{\beta}_j)$ , for estimate  $\beta_j$  which becomes more accurate with larger sample sizes. After each cohort, we sample many times from a normal distribution with parameters based on the estimate of  $\beta_j$  and its variance. These samples are then plugged into our dose-toxicity model to ascertain the probability of toxicity at the lowest dose. The trial will be recommended to stop if it breaks the rule based on the criteria above.

### 2.3.4 Operating Characteristics

Simulations were continually utilised during the design process of the trial to assess how various changes impact the overall performance. These changes to design features such as the sample size, weight function and stopping rules helped inform decisions which led to the final design.

Functions from pocrm package in R [22], [23] were modified in order to perform simulations and conduct the trial. The majority of work involved integrating the TITE component and the stopping rules into the code. In standard CRM designs a binary outcome for toxicity is generated for each patient based on a pre-specified true DLT rates for the dose they are assigned. Adding the TITE component means the time the toxicity occurs also has to be generated, the simulation must also track this time and incorporate this information into the PO-TITE-CRM model when it needs to make dose allocation decisions for the next cohort. We defined multiple scenarios to reflect various real life possibilities in order to assess the designs performance.

Standard scenarios to run involve adjusting the true DLT rates to reflect each dose being the TD25. For each of these we calculate the probability of selecting each dose as the TD25. It would be expected the dose with the highest probability of being selected has its true DLT rate set at 25% to match the target rate. A high probability of selection for the correct dose implies the design works well in the specified scenario. Additional characteristics such as the average number of patients at each dose level are also investigated. This can be used to look at how many patients may potentially be allocated to a toxic dose. It is also necessary to consider performance when all doses are too toxic, here we would want the design to recommend stopping early. Usually the true DLT rates used to define these scenarios abide by the monotonicity assumption. Due to the partial ordering we consider scenarios in which the

true DLT rates follow both orders. For trials with a large amount of orders it may be unfeasible to run so many simulations. However, as ADePT-DDR only has two orders we explored all scenarios for each ordering.

We simulated 10000 trials for each scenario using the finalised design detailed in section 2.3. Simulations were based on the assumption that the trial would recruit one patient per month. The occurrence of DLT's were randomly generated for patients in each cohort using a Bernoulli distribution with the probability set at the true DLT rate for the cohorts assigned dose level in the specific scenario. For patients who had a DLT occur, the time at which the DLT occurred was randomly generated using a uniform distribution which spanned the start of treatment to the end of follow-up. The simulations presented in Tables 2.3 and 2.4 took approximately 5 hours and 53 minutes to run. The Monte Carlo standard error for probabilities estimated by 10000 simulations is  $\sqrt{0.5 \times 0.5 / 10000} = 0.5\%$ .

Table 2.3 details simulations for eight scenarios to test the performance of the PO-TITE-CRM design using true DLT rates which reflect the first ordering. We analyse scenarios where each dose is the TD25 (scenarios 1-6) and when all doses are too toxic (scenario 8). Additionally, we also investigate performance under conditions where the probability of DLT is fairly similar between doses (scenario 7). This is a notoriously difficult circumstance for CRM designs to deal with as the limited number of patients and events at each dose make it hard to accurately estimate toxicity probabilities if they are similar. Simulation results for ordering 2 are shown in Table 2.4 where dose level 2a is considered more toxic than 2b. This is achieved by altering the true DLT rates so 2b has a lower probability of DLT compared to 2a.

Ideally we want the probability of selection for the dose allocated at TD25 to be as high as possible and greater than other dose levels. For scenarios 1-7 the TD25 is highlighted in bold along with results from the simulations.

However, for scenario 8 where all doses are too toxic we expect the trial to terminate early, here 'stop' should be selected and its associated probability of stopping is shown in bold.

TABLE 2.3: Operating Characteristics of the two-stage PO-TITE-CRM (with true DLT rates that imply 2b is more toxic than 2a) based on 10000 simulated trials. Definitions: DLT: Dose-limiting toxicity. P(select): Probability of selecting a dose as the TD25.

Scenario	Prior DLT	Dose Levels						Stop
		-1	0	1	2a	2b	3	
1: TD25 @-1	True DLT rate	0.25	0.4	0.45	0.5	0.55	0.6	0.0849
	P(select)	0.68	0.18	0.05	0.01	0	0	
	% of patients	39	32	20	6	3	0	
	Mean number of patients	10.17	8.46	5.33	1.67	0.69	0.07	
2: TD25 @0	True DLT rate	0.12	0.25	0.4	0.45	0.5	0.55	0.0079
	P(select)	0.23	0.51	0.2	0.03	0.02	0	
	% of patients	17	35	29	11	6	1	
	Mean number of patients	5.24	10.48	8.75	3.4	1.83	0.26	
3: TD25 @1	True DLT rate	0.09	0.12	0.25	0.4	0.45	0.5	4e-04
	P(select)	0.02	0.2	0.55	0.14	0.09	0.01	
	% of patients	4	20	34	23	16	3	
	Mean number of patients	1.22	6.41	10.97	7.23	5.14	1.02	
4: TD25 @2a	True DLT rate	0.06	0.09	0.12	0.25	0.4	0.45	1e-04
	P(select)	0	0.02	0.22	0.48	0.23	0.05	
	% of patients	1	12	20	31	25	11	
	Mean number of patients	0.47	3.88	6.74	10.43	8.2	3.5	
5: TD25 @2b	True DLT rate	0.03	0.06	0.09	0.12	0.25	0.4	0
	P(select)	0	0	0.02	0.3	0.43	0.25	
	% of patients	1	10	12	24	28	25	
	Mean number of patients	0.25	3.36	4.15	8.17	9.33	8.33	
6: TD25 @3	True DLT rate	0.01	0.03	0.06	0.09	0.12	0.25	0
	P(select)	0	0	0	0.09	0.13	0.78	
	% of patients	0	10	11	18	18	42	
	Mean number of patients	0.1	3.13	3.49	5.46	5.6	13.14	
7: Equal steps in DLT rate	True DLT rate	0.05	0.1	0.15	0.2	0.25	0.3	3e-04
	P(select)	0	0.03	0.12	0.31	0.28	0.26	
	% of patients	2	13	18	26	23	19	
	Mean number of patients	0.55	4.03	5.72	8.32	7.15	5.96	
8: All toxic	True DLT rate	0.5	0.6	0.65	0.7	0.75	0.8	0.7404
	P(select)	0.26	0	0	0	0	0	
	% of patients	56	26	15	2	0	0	
	Mean number of patients	9.05	4.27	2.4	0.37	0.04	0	

In scenarios 1 - 6 (Table 2.3), this design correctly selects the TD25 with probabilities between 43% and 78%, under the assumption 2b is more toxic than 2a. Likewise, for the ordering where 2a is more toxic than 2b, scenarios 9-14 (Table 2.4) have probabilities between 43% and 78% of correctly selecting

TABLE 2.4: Operating Characteristics of the two-stage PO-TITE-CRM (with true DLT rates that imply 2a is more toxic than 2b) based on 10000 simulated trials. Definitions: DLT: Dose-limiting toxicity. P(select): Probability of selecting a dose as the TD25.

Scenario	Prior DLT	Dose Levels						Stop
		-1	0	1	2a	2b	3	
9: TD25 @-1	True DLT rate	0.01	0.04	0.08	0.16	0.25	0.35	0.0827
	P(select)	0.25	0.4	0.45	0.55	0.5	0.6	
	% of patients	0.67	0.19	0.05	0	0.01	0	
	Mean number of patients	39	32	20	6	3	0	
10: TD25 @0	True DLT rate	10.19	8.43	5.27	1.6	0.68	0.07	0.0074
	P(select)	0.12	0.25	0.4	0.5	0.45	0.55	
	% of patients	0.23	0.52	0.2	0.02	0.02	0	
	Mean number of patients	18	36	29	11	6	1	
11: TD25 @1	True DLT rate	5.24	10.64	8.82	3.16	1.85	0.24	4e-04
	P(select)	0.09	0.12	0.25	0.45	0.4	0.5	
	% of patients	0.02	0.2	0.55	0.09	0.14	0.01	
	Mean number of patients	4	20	34	21	17	3	
12: TD25 @2a	True DLT rate	1.16	6.43	11.07	6.83	5.6	1.07	2e-04
	P(select)	0.06	0.09	0.12	0.25	0.15	0.45	
	% of patients	0	0.01	0.08	0.44	0.33	0.14	
	Mean number of patients	1	11	16	30	24	18	
13: TD25 @2b	True DLT rate	0.48	3.78	5.24	10.1	7.9	6.07	0
	P(select)	0.03	0.06	0.09	0.35	0.25	0.4	
	% of patients	0	0	0.15	0.31	0.43	0.11	
	Mean number of patients	1	11	18	30	28	14	
14: TD25 @3	True DLT rate	0.25	3.5	5.9	9.82	9.14	4.54	0
	P(select)	0.01	0.03	0.06	0.12	0.09	0.25	
	% of patients	0	0	0	0.13	0.09	0.78	
	Mean number of patients	0	10	11	19	16	43	
15: Equal steps in DLT rate	True DLT rate	0.1	3.13	3.51	5.88	5.06	13.13	2e-04
	P(select)	0.05	0.1	0.15	0.25	0.2	0.3	
	% of patients	0	0.02	0.12	0.32	0.27	0.26	
	Mean number of patients	2	13	19	27	22	18	
16: All toxic	True DLT rate	0.54	4.02	5.93	8.56	6.89	5.75	0.7273
	P(select)	0.5	0.6	0.65	0.75	0.7	0.8	
	% of patients	0.27	0	0	0	0	0	
	Mean number of patients	56	27	15	2	0	0	

the TD25. Correct selection probabilities are generally higher when the TD25 is at the first and last dose levels compared to dose levels 2a and 2b. However, these dose levels are still chosen with the highest probability as the TD25 in their given scenarios. For scenarios 7 and 15, the probabilities of toxicity are equally spaced, approximately 5% apart. This is a relatively difficult scenario for dose-finding studies to handle. The probability of selecting the TD25 is 28% and 32% for orderings 1 and 2 respectively and even if the performance is poor

the correct dose is still likely to be selected. In scenarios 8 and 16, where all the doses are too toxic, the design very seldom allocates patients higher than the first three doses and there is a high chance (74% and 73% respectively) that the trial will recommend early stopping.

Additionally, we assess designs based on how doses are allocated to patients. Designs may correctly select the TD however, this could be undesirable and unethical if the majority of patients are over dosed at the more toxic dose levels. The average number and the percentage of patients at each dose level, for each scenario, is recorded in Tables 2.3 and 2.4.

The percentage of patients treated at the TD25 ranges between 23% and 43% for each scenario under both orderings. The design also allocates the most patients on average to the TD25 apart from in scenario 7. In this case more patients were allocated to the next lowest dose, we have already discussed the difficulties of this scenario so this characteristic is not too concerning. The mean number of patients recruited for scenarios 1-6 is 26, 30, 32, 33, 34 and 31 respectively. Similarly for scenarios 9-14 its 26, 30, 32, 34, 33 and 31. Even though we allow for up to 60 patients the majority of trials terminate early based on the pre-defined rules for selecting the TD25. This information is presented in Table 2.5 which also shows how often the max sample size is reached from the 10000 trials for each scenario.

Overall, the simulation results show the specification of this design performs relatively well in a number of scenarios. We have shown there is a high probability of the trial stopping early if all dose-levels are too toxic. We have also shown the design behaves in an appropriate manner when there is a lack of disparity between dose-levels in terms of toxicity. Finally, we have demonstrated that regardless of the ordering we observe the PO-TITE-CRM has a

TABLE 2.5: Summary of simulated patient numbers for each scenario.

Scenario	Max no. of patients	% max reached	Mean no. of patients
1: TD25 @-1	60	0.21	26.38
2: TD25 @0	60	0.08	29.97
3: TD25 @1	60	0.05	32.01
4: TD25 @2a	60	0.12	33.22
5: TD25 @2b	60	0.06	33.60
6: TD25 @3	60	0.02	30.92
7: Equal steps	60	0.01	31.74
8: All toxic	54	0.01	16.14
9: TD25 @-1	60	0.17	26.24
10: TD25 @0	60	0.11	29.95
11: TD25 @1	60	0.06	32.15
12: TD25 @2a	60	0.07	33.56
13: TD25 @2b	60	0.03	33.16
14: TD25 @3	60	0.08	30.81
15: Equal steps	60	0.02	31.69
16: All toxic	51	0.01	16.11

high probability of selecting the correct dose. There are a number of limitations to the operating characteristics presented here which are due to the specification of the simulations and trial design. Section 2.4 explores and discusses these limitations in more detail.

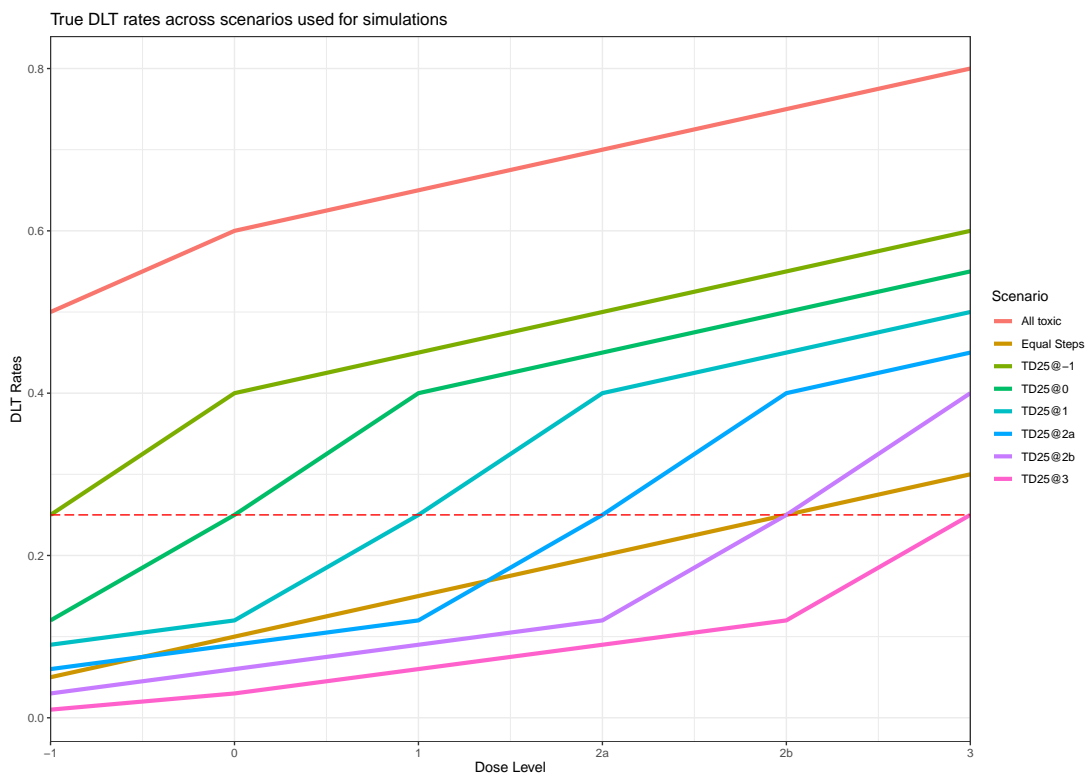
## 2.4 Exploring other designs

The operating characteristics presented in section 2.3.4 provide an insight into how the trial design operates and its effectiveness at selecting the TD25. However, several factors impact the results seen here. These factors can be grouped into two main categories, limitations with the simulations performed or the trial design.

To simulate various scenarios the true DLT rates are adjusted to reflect the TD25 being at different dose levels. There is no formal process to select these values as such their selection is fairly arbitrary. We set one dose level as the

TD25 with lower and higher dose levels set at lower and higher DLT rates respectively. Figure 2.4 illustrates the dose levels for scenarios in Table 2.3 where dose level 2b is more toxic than 2a. The DLT rates cover some possible scenarios and account for a range of plausible values. However, these true DLT rates may not accurately reflect what we observe once the trial begins. Also, the relationship between the rates and the dose levels may not be similar to what we use in the simulations. Multiple other scenarios could be investigated but it would still be impossible to account for all possible variations which may occur. Hence when evaluating the performance of a design it is important to note the scenario in which it is being evaluated and whether or not the design performs as expected and to an adequate level. For ADePT-DDR, the design produces reasonable operating characteristics under each scenario.

FIGURE 2.4: True DLT rates used for each of the scenarios where dose level 2b is more toxic than 2a. The dotted red line represents the target dlt rate of 25% (TD25).





The original methodological papers by Wages et al. [17], [18] only provide simulations for their examples using true DLT rates that are monotonically increasing which represented one of their possible orderings. We cannot tell how their design would perform under scenarios from different orderings. It is unclear as to why this wasn't examined. Initially, in ADePT-DDR we followed suit and only produced simulations under a monotonically increasing DLT rate (order where 2b is more toxic than 2a, Table 2.3). However, as we are unclear on the ordering of 2a and 2b there is a possibility that 2b is less toxic. So those initial simulations would not provide an accurate assessment of the design in that circumstance. This was the main motivation for running scenarios in Table 2.4, in which we see the design performs at a similar level regardless of the partial ordering. ADePT-DDR is a simple case of partial ordering as there are only two possible orderings and six dose-levels. For trials with higher numbers of orderings or dose-levels the number of scenarios that would have to be evaluated would increase which may be infeasible. Here it may be more beneficial to choose a handful of scenarios from multiple different orderings to cover a wider range of possible outcomes for the trial to assess the design.

There are various features in this trial design that impact how it performs. The partial ordering caused by dose levels 2a and 2b adds complexity to design. If one of these dose-levels were to be removed or a normal ordering was assumed a standard TITE-CRM design could be used instead. However, this would take away from what the trial is trying to discover. This trial also has a long follow-up period due to potential late-onset toxicities and in turn, will have a long duration. The TITE component will allow for the duration to be a lot shorter than it would be otherwise. TITE-CRM designs allow for patients to be recruited sequentially and allocated a dose based on available information from patients already in the trial. The design for ADePT-DDR uses cohorts of three and a minimum follow-up period. The dose-escalation decisions will

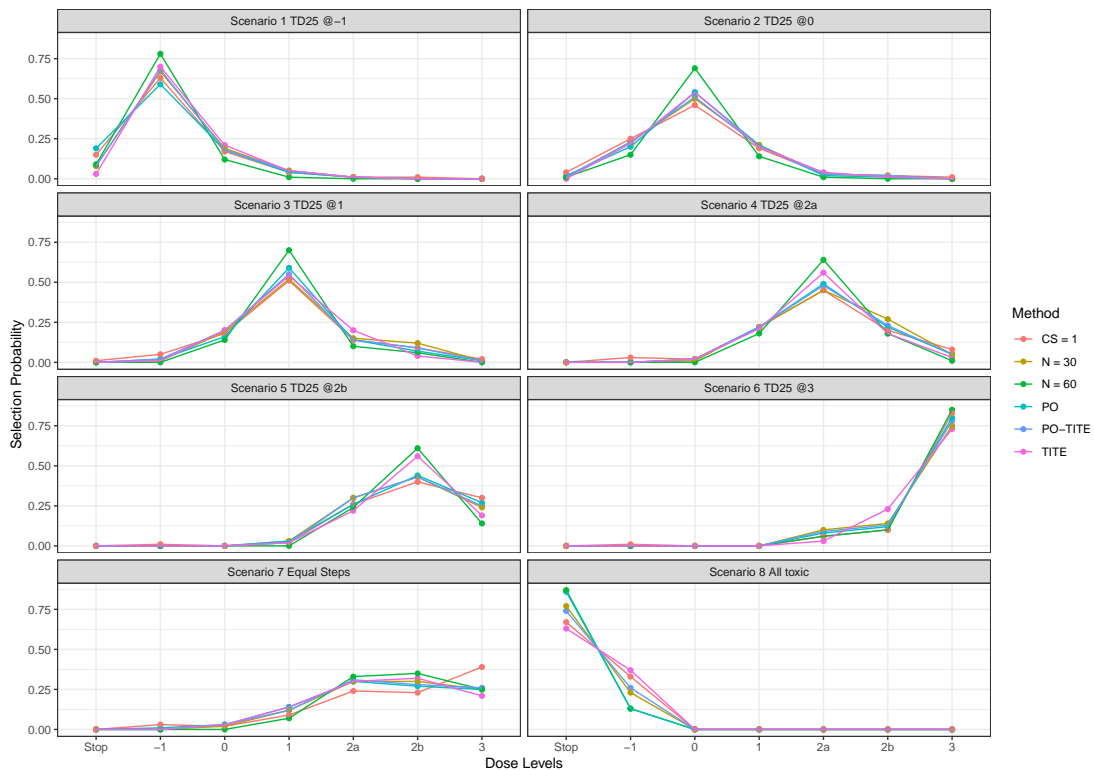
only be made every third patient after a specific amount of time. This is done for safety and practicality reasons but means that some patients may not be able to enter the trial and it also loses some of the benefits of the TITE-CRM. We also have a sample size of 60 patients but include a stopping rule for when a consensus is reached which means we often don't recruit the maximum sample size. Further simulations were produced to investigate how these features affected the trial. Tables 2.6 and 2.7 compares selection probabilities from the ADePT-DDR trial design with five alternative designs based on the two different orderings. Figures 2.5 and 2.6 visualise the result from each of these tables respectively. 10000 trials were simulated for each scenario which took 62 hours and 22 minutes to complete.

1. TITE-CRM design. This design assumes that partial ordering doesn't exist and that dose-level 2b is more toxic than 2a. A TITE-CRM is used instead of a PO-TITE-CRM. All other stopping rules and details remain the same.
2. PO (Partial Ordering design). This design removes the TITE component and uses a PO-CRM as detailed by [17]. This requires the removal of the minimum follow-up period so all dose allocation decisions are made once all 3 patients in a cohort have been observed for the full follow-up period of one year. All other stopping rules and details remain the same.
3.  $N = 30$ . This design uses a fixed sample size of 30 patients and removes the stopping rule for reaching consensus. The analysis is still conducted using the PO-TITE-CRM. All other stopping rules and details remain the same.
4.  $N = 60$ . This design uses a fixed sample size of 60 patients and removes the stopping rule for reaching consensus. The analysis is still conducted

using the PO-TITE-CRM. All other stopping rules and details remain the same.

5.  $CS = 1$ . This design uses a cohort size (CS) of one. All other stopping rules remain the same.

FIGURE 2.5: Plot of the simulation results presented in Table 2.6 detailing selection probabilities for multiple designs across scenarios 1-8 (where 2b is considered more toxic than 2a).



The TITE-CRM performs similarly to our original design for scenarios 1-8 where 2a is assumed less toxic than 2b (Table 2.3). Compared to the PO-TITE design we see increases in probability selection for scenarios 4 and 5 where the target dose is at 2a and 2b respectively. This increase in performance can be attributed to the fact that the partial ordering no longer exists as we have assumed an ordering. The lower selection probabilities for the PO-TITE-CRM can be seen as the price to pay for the uncertainty of not knowing the order of 2a and 2b. However, the TITE-CRM underperforms in scenarios 9-16 where 2a

TABLE 2.6: Selection probabilities of the TD25 and expected trial duration (in months) for the PO-TITE, TITE and PO-CRM designs as well as modified PO-TITE-CRM designs for scenarios 1-8 (where 2b is considered more toxic than 2a) based on 10000 simulated trials.

Scenario	CRM details	Prior DLT	Dose Levels						Stop	Duration	Mean N
			-1	0	1	2a	2b	3			
			0.01	0.04	0.08	0.16	0.25	0.35			
1: TD25 @-1		True DLT rate	0.25	0.4	0.45	0.5	0.55	0.6			
	PO-TITE	P(select)	0.68	0.18	0.05	0.01	0	0	0.08	57.61	26.38
	TITE	P(select)	0.7	0.21	0.05	0.01	0	0	0.03	59.55	27.46
	PO	P(select)	0.59	0.18	0.04	0.01	0	0	0.19	132.19	22.11
	N = 30	P(select)	0.67	0.19	0.05	0.01	0	0	0.08	60.02	27.72
	N = 60	P(select)	0.78	0.12	0.01	0	0	0	0.09	106.61	53.62
	CS = 1	P(select)	0.63	0.17	0.04	0.01	0.01	0	0.15	87.62	22.44
2: TD25 @0		True DLT rate	0.12	0.25	0.4	0.45	0.5	0.55			
	PO-TITE	P(select)	0.23	0.51	0.2	0.03	0.02	0	0.01	64.06	29.97
	TITE	P(select)	0.22	0.54	0.2	0.04	0.01	0		63.5	29.65
	PO	P(select)	0.2	0.54	0.21	0.02	0.01	0	0.02	163.53	27.79
	N = 30	P(select)	0.23	0.5	0.21	0.03	0.02	0	0.01	63.26	29.52
	N = 60	P(select)	0.15	0.69	0.14	0.01	0	0	0.01	116.29	59
	CS = 1	P(select)	0.25	0.46	0.19	0.03	0.02	0.01	0.04	105.41	27.59
3: TD25 @1		True DLT rate	0.09	0.12	0.25	0.4	0.45	0.5			
	PO-TITE	P(select)	0.02	0.2	0.55	0.14	0.09	0.01		67.74	32.01
	TITE	P(select)	0.01	0.2	0.54	0.2	0.04	0		64.44	30.18
	PO	P(select)	0.02	0.16	0.59	0.14	0.07	0.01		178.12	30.43
	N = 30	P(select)	0.01	0.19	0.52	0.15	0.12	0.01		64.04	29.96
	N = 60	P(select)	0	0.14	0.7	0.1	0.06	0		117.89	59.89
	CS = 1	P(select)	0.05	0.18	0.51	0.14	0.09	0.02	0.01	114.18	30.13
4: TD25 @2a		True DLT rate	0.06	0.09	0.12	0.25	0.4	0.45			
	PO-TITE	P(select)	0	0.02	0.22	0.48	0.23	0.05		69.91	33.22
	TITE	P(select)	0	0.02	0.21	0.56	0.18	0.03		66.99	31.59
	PO	P(select)	0	0.02	0.22	0.49	0.22	0.05		189.69	32.52
	N = 30	P(select)	0	0.01	0.22	0.45	0.27	0.05		64.1	29.99
	N = 60	P(select)	0	0	0.18	0.64	0.18	0.01		118.01	59.96
	CS = 1	P(select)	0.03	0.02	0.22	0.45	0.2	0.08		113.77	30.01
5: TD25 @2b		True DLT rate	0.03	0.06	0.09	0.12	0.25	0.4			
	PO-TITE	P(select)	0	0	0.02	0.3	0.43	0.25		70.6	33.6
	TITE	P(select)	0	0	0.02	0.22	0.56	0.19		68.34	32.34
	PO	P(select)	0	0	0.03	0.26	0.44	0.27		194.41	33.38
	N = 30	P(select)	0	0	0.03	0.3	0.43	0.24		64.11	29.99
	N = 60	P(select)	0	0	0	0.24	0.61	0.14		118.08	59.99
	CS = 1	P(select)	0.01	0	0	0.26	0.4	0.3		110.26	29
6: TD25 @3		True DLT rate	0.01	0.03	0.06	0.09	0.12	0.25			
	PO-TITE	P(select)	0	0	0	0.09	0.13	0.78		65.78	30.92
	TITE	P(select)	0	0	0	0.03	0.23	0.73		65.6	30.82
	PO	P(select)	0	0	0	0.08	0.12	0.8		183.48	31.4
	N = 30	P(select)	0	0	0	0.1	0.14	0.75		64.12	30
	N = 60	P(select)	0	0	0	0.06	0.1	0.85		118.09	60
	CS = 1	P(select)	0.01	0	0	0.06	0.1	0.83		92.92	23.98
7: Equal steps		True DLT rate	0.05	0.1	0.15	0.2	0.25	0.3			
	PO-TITE	P(select)	0	0.03	0.12	0.31	0.28	0.26		67.25	31.74
	TITE	P(select)	0	0.03	0.14	0.3	0.32	0.21		65.22	30.61
	PO	P(select)	0.01	0.03	0.14	0.3	0.27	0.25		186.6	31.96
	N = 30	P(select)	0	0.02	0.12	0.3	0.3	0.25		64.07	29.97
	N = 60	P(select)	0	0	0.07	0.33	0.35	0.25		118.04	59.97
	CS = 1	P(select)	0.03	0.02	0.09	0.24	0.23	0.39		101.81	26.55
8: All toxic		True DLT rate	0.5	0.6	0.65	0.7	0.75	0.8			
	PO-TITE	P(select)	0.26	0	0	0	0	0	0.74	39.19	16.14
	TITE	P(select)	0.37	0	0	0	0	0	0.63	44.65	19.17
	PO	P(select)	0.13	0	0	0	0	0	0.86	70.38	10.92
	N = 30	P(select)	0.23	0	0	0	0	0	0.77	41.35	17.34
	N = 60	P(select)	0.13	0	0	0	0	0	0.87	47.35	20.68
	CS = 1	P(select)	0.33	0	0	0	0	0	0.67	46.43	10.51

TABLE 2.7: Selection probabilities of the TD25 and expected trial duration (in months) for the PO-TITE, TITE and PO-CRM designs as well as modified PO-TITE-CRM designs for scenarios 9-16 (where 2a is considered more toxic than 2b) based on 10000 simulated trials.

Scenario	CRM details	Prior DLT	Dose Levels						Stop	Duration	Mean N
			-1	0	1	2a	2b	3			
			0.01	0.04	0.08	0.16	0.25	0.35			
9: TD25 @-1		True DLT rate	0.25	0.4	0.45	0.55	0.5	0.6			
	PO-TITE	P(select)	0.67	0.19	0.05	0	0.01	0	0.08	57.35	26.23
	TITE	P(select)	0.7	0.21	0.05	0	0	0	0.03	59.34	27.34
	PO	P(select)	0.58	0.17	0.04	0	0	0	0.2	131.46	21.98
	N = 30	P(select)	0.68	0.18	0.04	0	0.01	0	0.09	59.85	27.62
	N = 60	P(select)	0.78	0.13	0.01	0	0	0	0.09	106.5	53.56
	CS = 1	P(select)	0.62	0.16	0.05	0	0.01	0	0.15	87.6	22.43
10: TD25 @0		True DLT rate	0.12	0.25	0.4	0.5	0.45	0.55			
	PO-TITE	P(select)	0.23	0.52	0.2	0.02	0.02	0	0.01	64.02	29.95
	TITE	P(select)	0.21	0.56	0.19	0.02	0.01	0		63.57	29.69
	PO	P(select)	0.2	0.54	0.2	0.01	0.02	0	0.02	163.06	27.7
	N = 30	P(select)	0.24	0.51	0.2	0.02	0.03	0	0.01	63.35	29.57
	N = 60	P(select)	0.15	0.7	0.13	0	0.01	0	0.01	116.22	58.96
	CS = 1	P(select)	0.25	0.47	0.19	0.02	0.03	0.01	0.04	105.04	27.49
11: TD25 @1		True DLT rate	0.09	0.12	0.25	0.45	0.4	0.5			
	PO-TITE	P(select)	0.02	0.2	0.55	0.09	0.14	0.01		68	32.15
	TITE	P(select)	0.01	0.22	0.58	0.14	0.04	0		64.86	30.41
	PO	P(select)	0.03	0.17	0.59	0.09	0.12	0.01		177.68	30.35
	N = 30	P(select)	0.02	0.2	0.51	0.1	0.16	0.01		64.03	29.95
	N = 60	P(select)	0	0.14	0.71	0.05	0.1	0		117.88	59.88
	CS = 1	P(select)	0.05	0.17	0.53	0.09	0.13	0.02	0.01	113.98	30.07
12: TD25 @2a		True DLT rate	0.06	0.09	0.12	0.25	0.15	0.45			
	PO-TITE	P(select)	0	0.01	0.08	0.44	0.33	0.14		70.52	33.56
	TITE	P(select)	0	0.02	0.14	0.26	0.45	0.14		67.23	31.73
	PO	P(select)	0.01	0.02	0.09	0.45	0.28	0.15		194.42	33.38
	N = 30	P(select)	0	0.01	0.08	0.42	0.35	0.14		64.09	29.98
	N = 60	P(select)	0	0	0.03	0.57	0.33	0.07		117.98	59.94
	CS = 1	P(select)	0.02	0.01	0.07	0.4	0.32	0.18		113.02	29.8
13: TD25 @2b		True DLT rate	0.03	0.06	0.09	0.35	0.25	0.4			
	PO-TITE	P(select)	0	0	0.15	0.31	0.43	0.11		69.8	33.16
	TITE	P(select)	0	0.01	0.26	0.36	0.28	0.1		65.95	31.02
	PO	P(select)	0	0.01	0.14	0.34	0.43	0.1		190.68	32.7
	N = 30	P(select)	0	0	0.15	0.3	0.44	0.11		64.12	30
	N = 60	P(select)	0	0	0.1	0.29	0.57	0.04		118.07	59.99
	CS = 1	P(select)	0.02	0	0.14	0.27	0.4	0.17		112.27	29.58
14: TD25 @3		True DLT rate	0.01	0.03	0.06	0.12	0.09	0.25			
	PO-TITE	P(select)	0	0	0	0.13	0.09	0.78		65.58	30.81
	TITE	P(select)	0	0	0	0.04	0.21	0.74		65.66	30.86
	PO	P(select)	0	0	0	0.13	0.07	0.8		183.9	31.47
	N = 30	P(select)	0	0	0	0.13	0.11	0.75		64.12	30
	N = 60	P(select)	0	0	0	0.09	0.06	0.85		118.09	60
	CS = 1	P(select)	0.01	0	0	0.1	0.07	0.82		93.1	24.03
15: Equal steps		True DLT rate	0.05	0.1	0.15	0.25	0.2	0.3			
	PO-TITE	P(select)	0	0.02	0.12	0.32	0.27	0.26		67.17	31.69
	TITE	P(select)	0	0.03	0.19	0.27	0.28	0.24		65.01	30.49
	PO	P(select)	0	0.03	0.16	0.32	0.26	0.23		186.35	31.92
	N = 30	P(select)	0	0.02	0.13	0.3	0.29	0.25		64.1	29.99
	N = 60	P(select)	0	0	0.07	0.36	0.31	0.25		117.97	59.94
	CS = 1	P(select)	0.03	0.02	0.09	0.23	0.23	0.4		102.22	26.67
16: All toxic		True DLT rate	0.5	0.6	0.65	0.75	0.7	0.8			
	PO-TITE	P(select)	0.27	0	0	0	0	0	0.73	39.14	16.11
	TITE	P(select)	0.37	0	0	0	0	0	0.63	44.23	18.94
	PO	P(select)	0.13	0	0	0	0	0	0.87	69.79	10.81
	N = 30	P(select)	0.23	0	0	0	0	0	0.77	41.18	17.24
	N = 60	P(select)	0.13	0	0	0	0	0	0.87	47.29	20.64
	CS = 1	P(select)	0.33	0	0	0	0	0	0.67	45.76	10.31

FIGURE 2.6: Plot of the simulation results presented in Table 2.7 detailing selection probabilities for multiple designs across scenarios 9-16 (where 2a is considered more toxic than 2b).



is assumed more toxic than 2b. Specifically, scenarios 12 and 13 where it fails to identify the TD25 the majority of the time.

The PO-CRM design without a TITE component also performs similarly except for scenarios 1, 8, 9 and 16 where the trial stops more regularly for excess toxicity at the lowest dose. This would be because patients complete the full follow-up window before the next dose allocation decision is made. In a TITE setting a new cohort could be recruited before patients in previous cohorts experience a DLT. The main difference between these designs is the trial duration. Without the TITE component the trial duration is significantly longer, with the average length ranging from 70 to 195 months compared to 39 to 71 months for PO-TITE-CRM.

The design with a fixed sample size of 30 performs is comparable to our design with the sample size of 60 and the consensus stopping rule. With a sample size of 30 selection probabilities are only 2-5% lower. For the design with 60 patients, we see much improved operating characteristics with selection probabilities ranging from 31% to 85% for the various scenarios. Even though our original design specifies a sample size of 60 we rarely ever reach it as we often stop for consensus hence why this design performs better. The trade-off here is trial duration. Recruitment and follow-up under the constraints of these simulations will take much longer compared to our specification which is not ideal for an early-phase trial. Originally our design had a fixed sample size of 30 but as the clinicians wanted a dose expansion cohort we opted to use the consensus rule to ensure a minimum number of patients would be treated at the TD25.

For the design with no cohorts, or cohort size of one, we see somewhat comparable performance to that of the PO-TITE-CRM design. The design performs similarly for scenarios where the TD25 is at the lowest or highest dose level but underperforms for the more complex scenarios in terms of selection probabilities. This discrepancy in performance may be related to how the simulations recruit patients into the trial and the large DLT follow-up period. Meaning more frequent dose allocation decisions are being made each with less available information. This also leads to the no cohorts design having a longer duration. Patients entered into the trial in cohorts of three won't having to wait the full minimum follow-up period between patients within the cohort.

## 2.5 Discussion

The PO-CRM and PO-TITE-CRM designs offer solutions to the issue of partial ordering where the order of the treatments is only partially known. The original methodology details that this issue commonly arises in trials of multiple agents, where each drug individually may follow the monotonicity assumption but when combined at certain dose levels this may not hold. This issue is typically dealt with by fixing the dose of one of the agents and escalating in the other or escalating in both agents simultaneously. This means certain drug combinations that are clinically relevant may not be investigated or even considered.

Here we have shown that these issues can also arise in other situations. Even though the ADePT-DDR trial uses multiple agents the issue of partial ordering still occurs due to the varying treatment dose and schedule for one of its agents AZD6738. Implementing the PO-TITE-CRM design allowed us to deal with this issue effectively. There may be other factors or variables in single-agent dose-finding trials that would lead to the issue of partial ordering and would warrant the use of either PO-CRM or PO-TITE-CRM. The small literature review conducted highlighted this may be the first instance of the PO-TITE-CRM design being applied. It is important to note that although this methodology takes into account all the various orderings the main aim is to identify the TD and does not attempt to identify the order that is more correct.

Compared to other CRM based designs only a few additional pieces of information are required to implement the PO-CRM design. More importantly is the number of toxicity orderings and prior probabilities for the orders. Dependent on how many dose combinations are available it may not be feasible to investigate all combinations and all orderings. Careful thought and consideration should be given to the combinations and orderings selected which would



require input from all relevant investigators. In terms of priors for orderings if no prior information is available all orders should be treated as equally likely to occur. Extending this design to the PO-TITE-CRM requires a fit for purpose weight function and is applied similarly to the TITE-CRM methodology. There is an R package available with functions that can be used to run and simulate a PO-CRM trial. These functions were extended to include weighted dose toxicity models as described in this chapter to implement PO-TITE-CRM into ADePT-DDR. The lack of available software for PO-TITE-CRM specifically may be one of the reasons for its lack of use.

In terms of ADePT-DDR, dose combinations were decided upon by the clinical investigators. The issue of partial ordering was due to the dose-levels 2a and 2b as such this methodology was employed to deal with that scenario. Meaning that this is a very simple example of partial ordering as we only have two possible orderings and six dose levels. The necessity of implementing this methodology was discussed and whether or not adopting an easier solution by simply altering the dose levels would have been better. Ultimately, the dose levels selected by the clinicians were deemed the most relevant with the TD25 likely to be one of these doses.

Simulations and operating characteristics were the main tools used to assess the designs performance as well as help understand the impact of sample size and stopping rules. This was an iterative process that involved running multiple iterations of simulations under various scenarios until the design was finalised. A key point is that scenarios from simulations should account for each of the possible orderings. ADePT-DDR only has two orderings, we ran scenarios for both. For a trial with a greater number of orderings, this may be unfeasible but at least some scenarios should be assessed to ensure the design is behaving as expected. Overall, the design operating characteristics performed reasonably well even in difficult scenarios.

One limitation of the simulations is how the time-to-event data is generated. The time of DLTs is sampled from a uniform distribution  $U(0, 413)$ , where the time of the DLT can occur at any time between the patient beginning treatment and the end of follow-up (413 days). Using this uniform distribution implies that a DLT has an equal probability of occurring at any time-point in the observation window. This may not be an accurate representation of what happens in the actual trial. Similar comments can be made about the accrual rate used in the simulations. Here we specified the recruitment of one patient per month which is in no way guaranteed for the actual trial. Wages et al. [18], when presenting this methodology investigated four different applications of the PO-TITE-CRM which used different models to enroll patients and allocate DLTs. Results across these four applications were comparable.

The simulations are also able to instantaneously determine dose-levels for incoming cohorts with all available information. This does not fully reflect the process in which dose-escalation decisions would be made during the actual running of the trial. The analysis would require a data snapshot and time would have to be spent cleaning the data and determining the next dose-level. Meaning any data from the point of the snapshot would not be included in any dose escalation/de-escalation decisions.

Similarly, there may also be limitations with some of the design choices made concerning to cohort size and sample size. These were investigated alongside a variety of other trial designs that could have been implemented. This was done to validate the choices we made with the design and highlight the differences in operating characteristics due to the varying assumptions and components in the designs. The standard PO-CRM had a much longer average duration due to the lack of TITE component whereas a standard TITE-CRM overall performs better but assumes the ordering of toxicity is known.

## 2.6 Conclusion

The monotonicity assumption may not hold in some dose-finding trials leading to the issue of partial ordering. This could be due to multiple-agents being investigated or varying factors in single-agent treatment. PO-CRM and PO-TITE-CRM are important trial designs as they address this core issue. ADePT-DDR is a platform trial with its initial component being a dose-finding trial investigating AZD6738 in combination with radiotherapy, of which the toxicity ordering for two of the dose levels for investigation is unknown. The PO-TITE-CRM design allows for us to deal with this issue of partial ordering as well as account for potential late-onset toxicities due to radiotherapy with its TITE component.

We detail the issue of partial ordering and how we implemented the trial design, in what we believe is the first real-world application of this design. A large amount of simulation work is required to assess the performance of the design. This is often an iterative process to refine decisions that were made and often requires input from both clinical and statistical investigators. We recommend running several varied scenarios for each potential ordering that will be investigated. Finally, we also compared the implementation of PO-TITE-CRM to various other designs.



## Chapter 3

# Extensions to the Wages and Tait trial design

### 3.1 Introduction

Typically the main aim of Phase I clinical trials is to identify the maximum tolerated dose (MTD) of the treatment being investigated. The MTD is usually determined under the cytotoxic assumption which assumes the most toxic dose is the most efficacious. With model based designs such as the continual reassessment method (CRM) [10] escalation occurs to identify the dose with an associated probability of toxicity based on a pre-defined target. Dose selection and escalation decisions do not consider efficacy rather they are determined based on the occurrence of toxicities. The cytotoxic assumption here implies that rate of efficacy increases monotonically with the probability of toxicity and dose level. Subsequent Phase II trials aim to assess the efficacy of the treatment at the recommended dose (MTD). Usually these two phases are conducted independently of each other and as such the ability to share information across the phases is somewhat lost.

For treatments like chemotherapy which kills all cells including cancer cells

the cytotoxic assumption is valid. However, the emergence of modern treatments such as immunotherapy and molecular targeted agents challenges this paradigm. Immunotherapy is a form of treatment which utilises the body's own immune system to fight the cancer. Molecular targeted agents work by interfering with specific molecules responsible for the growth, spread and progression of cancer. The monotonic assumption of dose-toxicity and dose-efficacy may not hold for these new types of treatments. Furthermore, these treatments in general are less toxic than traditional cytotoxic agents such as chemotherapy therefore it is possible the most efficacious dose may occur at a dose level below the MTD [29]. This produces some methodological challenges for dose-finding trials. Instead of trying to identify the MTD the goal would be to determine the optimal biological dose (OBD). Depending on the aims of the trial and the design implemented the definition of the OBD may vary. The OBD could be a dose that provides the maximum probability of efficacy with the probability of toxicity being less than a pre-defined target value, or the dose that has a beneficial trade-off between toxicity and efficacy. In order to determine an optimal dose both toxicity and efficacy outcomes need to be considered, this leads to a need for joint phase I/II trial designs. Here we will briefly explore some of these designs.

Braun [30] proposed the bivariate continual reassessment method (bCRM), an extension to the CRM which incorporates competing outcomes for both toxicity and disease progression. The design models the probabilities of toxicity and progression independently, it is suggested that either empiric, logistic and hyperbolic tangent functions are used dependent on their biological plausibility. Both outcomes are then combined into a joint distribution which is used to estimate posterior means based on priors and observed data.

Thall & Cook [31] developed EffTox, a Bayesian adaptive dose-finding trial based on trade-offs between the probabilities of toxicity and efficacy. Marginal

probabilities of efficacy and toxicity at each dose are modelled and used with utility contours to determine the desirability of each dose based on posterior probabilities of efficacy and toxicity [32].

Zhou et al. [33] introduced a Utility-based Bayesian Optimal Interval (U-BOIN) phase I/II design to identify the OBD. This design is an extension of the Bayesian optimal interval (BOIN) design for phase I trials developed by Liu and Yuan [19]. U-BOIN jointly models toxicity and efficacy with a multinomial-Dirichlet model and uses a utility function to measure the dose risk-benefit trade-off. The design consists of two seamless stages. Firstly, in stage I the BOIN design is used to explore the dose levels and determine a set of admissible doses and collect preliminary efficacy data. In stage II posterior estimates of utility for each dose are continuously updated after each cohort this is done using toxicity and efficacy data from both stages.

Zhang et al. [34] introduced the trivariate CRM (TriCRM) design. The design considers patients to have one of three possible outcomes: no efficacy and toxicity, efficacy without toxicity and toxicity. These outcomes are then modelled using a continuation-ratio model. A Bayesian approach and dose-finding algorithm is then used to identify the OBD similar to the CRM.

Anathakrishnan et al. [35] produced extensions to the modified Toxicity Probability Interval (mTPI) design by Ji & Wang [36] and Toxicity Equivalent Range (TEQR) design by Blanchard & Longmate [37] to include efficacy outcomes. In both designs isotonic regression is applied to the observed DLT rates at the end of the trial. Dependent on the shapes of the dose-response curves and the underlying response rates isotonic regression is applied on the observed response rates or the differences in observed response rates to determine the optimal dose.

Riviere et al. [38] developed a Bayesian dose-finding design for MTA. The design works on the premise that for MTA efficacy initially increases with dose

then eventually plateaus. They use a logistic model with a plateau parameter to capture the dose-level at which plateaus begin in the dose-efficacy relationship. A weighted likelihood approach is also used to accommodate for any potential late-onset toxicities. This methodology incorporates adaptive randomisation to allocate dose-levels close to the likely plateau point.

This chapter revolves around the seamless phase I/II dose-finding adaptive design by Wages and Tait [39], that we will refer to as the WT design. This design models toxicity and efficacy independently. To model the probability of efficacy a set of possible efficacy skeletons are considered which would correspond to plausible dose-efficacy relationships. For the class of dose-efficacy models a single parameter model is used similar to the empiric model of the CRM. The authors recommend that  $(2n - 1)$  efficacy skeletons are specified where  $n$  is the number of doses being investigated. Toxicity is modelled using a CRM approach with an empiric model. As such a skeleton for toxicity is also required for this design. The dose-finding operates in two stages the adaptive randomisation (AR) phase and the maximisation phase. In the AR phase patients are adaptively randomised amongst a set of tolerable doses, where probabilities of randomisation to each dose are proportional to their posterior probabilities of efficacy. A pre-defined number of patients enter the AR phase and once recruitment has completed we move to the maximisation phase. In this phase patients are allocated to the dose in the tolerable set which maximises probability of efficacy.

The incorporation of an AR phase early on into the trial is beneficial since there may be a lack of data in order to rely on decisions made by the maximisation of efficacy probabilities. Also there may be doses that haven't been tested and randomisation allows for information to be collected from these. It also helps avoid getting stuck repeatedly recruiting to the same dose and allows for a more broad understanding of the dose-efficacy and toxicity relationships.



One extension we propose is the inclusion of randomisation to a control arm into the design. This would provide a set of patients who receive standard of care to act as controls and allow for comparisons to be made with outcomes from patients receiving the OBD. There is also the added benefit of being able to include standard of care into the models to get a better understanding of the dose-efficacy and toxicity relationships.

In Section 3.2, details the statistical aspects of the WT design and how it works. We introduce our extension to the design to include randomisation to control in Section 3.3. Section 3.4 evaluates the performance of the new design with a simulation study. Finally, discussions and conclusions are presented in Sections 3.5 and 3.6 respectively.

## 3.2 The Wages and Tait Design

In this section we detail the Wages and Tait design following the introduction of some notation. A set of  $I$  doses under investigation can be denoted as  $\mathcal{D} = \{d_1, \dots, d_I\}$ . For each patient  $j$  entered into the trial they are allocated to a dose level and joint outcomes for toxicity and efficacy are measured. The dose for the  $j$ th patient,  $X_j, j = 1, \dots, n$  can be thought of as random, taking values  $x_j \in \mathcal{D}$ . Let  $Y_j$  and  $Z_j$  be the random variables for binary toxicity and efficacy events respectively. For an individual patient  $j$  toxicity and efficacy outcomes can take values  $y_j, z_j \in \{0, 1\}$  where 0 indicates and event didn't happen and 1 indicates that it did.

Wages and Tait [39] utilise the CRM approach of O'Quigley et al. [10] to model toxicity. A univariate Bayesian method is used which begins by assuming a monotonically increasing dose-toxicity curve. The DLT probabilities,  $\pi_T(d_i)$ , are modelled at each dose level  $i$  where  $i = 1, \dots, I$ . The power model is specifically used by Wages and Tait in this design given by

$$F(d_i, \beta) = p_i^{\exp(\beta)} \quad (3.1)$$

A working model or skeleton containing the prior beliefs of toxicity at each dose level are provided by investigators in the form  $0 < p_1 < \dots < p_I < 1$ . For the single parameter in the power model  $\beta$  we assume it has a prior distribution  $g(\beta)$ . After the inclusion of  $j$  subjects into the trial, we have data in the form of  $\Omega_j = \{(x_1, y_1, z_1), \dots, (x_j, y_j, z_j)\}$ . The toxicity data can be used with Equation 3.1 to give the likelihood for  $\beta$

$$L(\beta|\Omega_j) = \prod_{l=1}^j \{F(x_l, \beta)\}^{y_l} \{1 - F(x_l, \beta)\}^{1-y_l} \quad (3.2)$$

the posterior density for  $\beta$  can be calculated using

$$P(\beta|\Omega_j) = \frac{L(\beta|\Omega_j)g(\beta)}{\int_{-\infty}^{\infty} L(\beta|\Omega_j)g(\beta)d\beta}. \quad (3.3)$$

This can then be use to establish the posterior mean of  $\beta$

$$\hat{\beta}_j = \int_{-\infty}^{\infty} \beta P(\beta|\Omega_j)d\beta \quad (3.4)$$

Using  $\hat{\beta}_j$  estimates of DLT probabilities at each dose level can be obtained via

$$\hat{\pi}_T(d_i) = F(d_i, \hat{\beta}_j) = p_i^{\exp(\hat{\beta}_j)}. \quad (3.5)$$

For a specific maximum acceptable toxicity rate  $\phi_T$  a set of acceptable or admissible doses can be declared as follows

$$\mathcal{A}_j = \{d_i : \hat{\pi}_T(d_i) \leq \phi_T; i = 1, \dots, I\}. \quad (3.6)$$

To model efficacy a Bayesian approach is taken similar to how toxicity was modelled but rather than using a singular working model a class of working models are considered. They use a class of skeletons which correspond to various dose-efficacy relationships. These relationships might be monotonically increasing (as dose increases efficacy increases), unimodal (initially increasing then decreasing) or plateau (initially increase then level off). As a guide it is suggested that  $(2I - 1)$  working models should be specified. The probability of an efficacious response at dose  $d_i$  is denoted as  $\pi_E(d_i)$ . The primary aim of the trial is to identify the optimal dose  $d_v \in \mathcal{D}$  which is defined such that

$$\pi_E(d_1) \leq \dots \leq \pi_E(d_v) \geq \dots \geq \pi_E(d_I). \quad (3.7)$$

Let  $K$  denote the number of efficacy skeletons being used. Then for each skeleton  $k$  we have  $0 < q_{1k} < \dots < q_{Ik} < 1$  and for a particular skeleton  $k; k = 1, \dots, K$  the true probability of efficacious response  $\pi_E(d_i)$  at  $d_i$  is modelled by

$$\pi_E(d_i) = \Pr(Z_j = 1 | d_i) \approx G_k(d_i, \theta) = q_{ik}^{\exp(\theta)} \quad (3.8)$$

As with the modelling of toxicity the power model is used again. Similarly as with  $\beta$  a prior distribution  $h(\theta)$  is assumed for  $\theta$ . For both the toxicity and efficacy models a Normal prior is used as first suggested by O'Quigley and Shen [28] such that  $\beta, \theta \sim N(0, 1.34)$ . Additionally for the modelling of efficacy prior information regarding the plausibility of each model is taken into account using a weight function  $v(k) = \{v(1), \dots, v(K)\}$ , where  $v(k) \geq 0$  and where  $\sum_k v(k) = 1$ . If no information is available a discrete uniform distribution can be specified for  $v(k)$ . After  $j$  patients have been included and observed in the study we have efficacy data from  $\Omega_j$  and the likelihood model under  $k$  is given by

$$L(\theta|\Omega_j) = \prod_{l=1}^j \{G_k(x_l, \theta)\}^{z_l} \{1 - G_k(x_l, \theta)\}^{1-z_l} \quad (3.9)$$

the posterior density is

$$P(\theta|\Omega_j) = \frac{L(\theta|\Omega_j)h(\theta)}{\int_{-\infty}^{\infty} L(\theta|\Omega_j)h(\theta)d\theta} \quad (3.10)$$

and under skeleton  $k$  the posterior mean is given by

$$\hat{\theta}_{jk} = \int_{-\infty}^{\infty} \theta P(\theta|\Omega_j)d\theta. \quad (3.11)$$

This information can be used to establish posterior model probabilities

$$w(k|\Omega_j) = \frac{v(k) \int_{-\infty}^{\infty} L_k(\theta|\Omega_j)h(\theta)d\theta}{\sum_{k=1}^K v(k) \int_{-\infty}^{\infty} L_k(\theta|\Omega_j)h(\theta)d\theta} \quad (3.12)$$

The posterior model probabilities are then used to determine which skeleton will be selected to model the dose-efficacy relationship. Each time a new patient is to be entered into the study and a dose-escalation decision needs to be made, the skeleton  $k^*$  with the largest posterior probability is selected such that

$$k^* = \arg \max_k w(k|\Omega_j). \quad (3.13)$$

After determining the best skeleton and calculating the posterior mean of  $\theta$  estimates of efficacy probabilities are then generated for each dose.

$$\hat{\pi}_E(d_i) = G_{k^*}(d_i, \hat{\theta}_{jk^*}) \quad (3.14)$$

Dose-finding is conducted in two stages. The first stage begins with the adaptive randomisation (AR) phase. Here the next dose is randomly selected from the set of admissible doses. Randomisation probabilities for each dose are

proportional to  $\hat{\pi}_E(d_i)$  so that doses with higher estimated efficacy are more likely to be assigned to patients. For doses in  $\mathcal{A}_j$  their adaptive randomisation probability  $R_i$  is

$$R_i = \frac{\hat{\pi}_E(d_i)}{\sum_{d_i \in \mathcal{A}_j} \hat{\pi}_E(d_i)}. \quad (3.15)$$

The AR phase lasts for a subset of  $j_R$  patients such that  $j_R \leq J$ , where  $J$  is the total number of patients to be entered into the trial. Wages and Tait suggest as a general rule of thumb to allocate 50% of patients to both stages. It was shown that this approach works well in a variety of scenarios. However, this can be easily be adapted to suit individual trials.

Once the AR phase has been completed the design switches to the second stage called the maximisation phase. Here the next dose is the dose from the admissible set with the highest estimated probability of efficacy. For a dose-escalation decision that needs to be made in the maximisation phase for the  $(j + 1)$ th patient the dose  $x_{j+1}$  is selected from the admissible set of doses  $\mathcal{A}_j$  with the highest estimated efficacy probability  $\hat{\pi}_E(d_i)$  i.e.

$$x_{j+1} = \arg \max_{d_i \in \mathcal{A}_j} \hat{\pi}_E(d_i) \quad (3.16)$$

The design also incorporates stopping rules for safety and futility. The safety rule stops the trial if too much toxicity is observed at the lowest dose level. This rule is applied throughout the trial for each dose-escalation decision. Exact binomial 95% confidence intervals are calculated for the lowest dose. The lower bound of the interval is then compared to the acceptable toxicity rate  $\phi_T$ . If the lower bound interval is greater than the acceptable rate it can be said that the treatment is too toxic to warrant further investigation. Patients need to have been observed at the lowest dose in order for this rule to trigger, if there is no data available at the lowest dose the binomial confidence

interval is effectively 0.

The futility rule stops the trial if there are too few observed efficacy events. This rule only comes into play during the maximisation phase. This rule uses a similar method to the stopping rule by utilising binomial 95% confidence intervals. During the maximisation phase the dose with the highest probability of efficacy is selected. At this point the 95% binomial confidence interval is calculated for the current dose and if the upper bound is less than the futility threshold  $\phi_E$  the trial is stopped as the treatment is inefficacious at all doses. Although 95% confidence intervals are used by Wages and Tait these can be altered accordingly.

### 3.3 RtC-WT: An extension to the Wages and Tait Design

In this section we introduce our proposed extension to the Wages and Tait (WT) design named Randomisation to Control Wages and Tait (RtC-WT). As the name states, the design will allow investigators to utilise the WT design with the ability to recruit patients to a control arm. This idea was initially conceived by Kristian Brock (KB) whilst working on the design of a new dose-finding trial.

#### 3.3.1 The Rationale for Incorporating Randomisation to Control

As a seamless phase I/II design WT is relatively simple and effective. The familiarity of using a CRM design to model toxicity and naturally extending that methodology to model efficacy with multiple working models mean the design is not particularly difficult to implement. The mathematics behind the

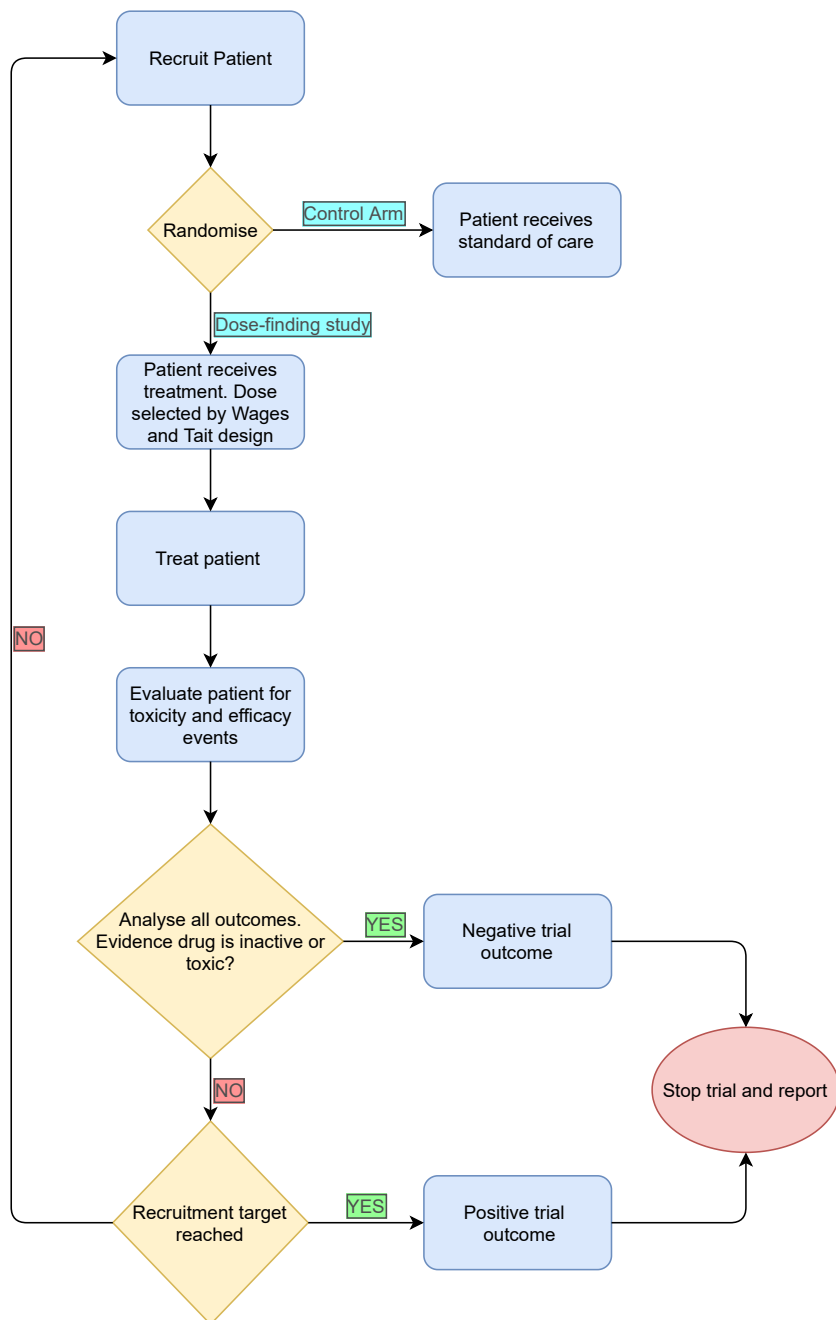
design is also not too intense so extensive computation won't be necessary. Given some effort this design could be implemented in a variety of programming languages although KB offers an easy implementation of this design in his R package *escalation* [40]. Considering all these factors extensions to this design can be executed without too many obstacles.

The WT design can be considered fairly unique due to its use of adaptive randomisation. Whilst the adaptive randomisation is not the core focus of the design it is still a distinguishing factor which could be leveraged to help investigators answer questions other designs can't. Specifically, the randomisation allows for more dose-levels to be explored and perhaps obtain a better understanding of the dose-toxicity and efficacy relationships.

Conceptually the WT design could include a control arm without any modification to the design. All that this would require is the addition of a new dose-level at which patients receive control treatment / standard of care. This would need to be implemented as the lowest dose-level as dose-levels still need to obey the monotonicity assumption for toxicity. The issue with taking this approach is that the design is unlikely to allocate patients to the control dose-level. Even though adaptive randomisation is in play the randomisation probabilities are based on estimates of efficacy probabilities and control patients may be unexpected to have an efficacious event. This is a desirable characteristic when investigating treatments as we don't want to allocate too many patients to inefficacious doses. However, if the aim is to establish a cohort of patients as controls to facilitate comparisons to the OBD this is not an optimal characteristic.

There is another approach which could also be used to include a control arm rather than our proposed design RtC-WT. A two arm randomised design could be used where patients are allocated to either the control arm or the dose-finding arm. Those patients allocated in the dose-finding arm will then

FIGURE 3.1: Flowchart of how a two arm randomised dose-finding design would operate using the Wages and Tait design.



be apart of the WT design see Figure 3.1. This approach maintains many of the traditional qualities of a two-arm randomised trial. The number of patients in each arm can be specified this way we guarantee a minimum number of patients in our control arm. Also, the characteristics of patients in both arms



are likely to be similar which would be beneficial when making comparisons between the two arms. A downside of this method is that the data for control patients is no longer included in the modelling process. Whilst control patients may still be observed for efficacious and toxic events these won't be included in the modelling as such the ability to make inferences on the dose-toxicity and efficacy relationships in reference to a control/ standard of care dose is lost.

Both of these approaches have their own merit but also have flaws as well. RtC-WT is somewhat of a middle ground which aims to recruit patients to a control dose and include the control patients data in the modelling process all whilst maintaining reasonable operating characteristics. We detail RtC-WT in Section 3.3.2 and explore the operating characteristics of this design in Section 3.4.

### 3.3.2 Design of the Proposed Extension RtC-WT

With this extension much of the Wages and Tait design stays the same. The modification only impacts the adaptive randomisation (AR) phase and requires some additional specification at the start of the trial. Firstly, we set the lowest dose-level  $d_1$  to be the control dose-level. This dose-level should be included in the working models for efficacy and toxicity and should be treated like any other dose-level. Even if toxicity and efficacy events are expected to be non-existent for control its important that their corresponding skeleton values are non-zero. Investigators also need to consider a randomisation probability  $\phi_R$  for the control dose. During the AR phase  $\phi_R$  represents the probability of selecting the control dose as the next dose level. The probability of randomisation  $R_i$  for other dose in  $\mathcal{A}_j$  is scaled accordingly such that the  $\sum_{d_i \in \mathcal{A}_j} R_i = 1$ . The adaptive randomisation probabilities can now be expressed as

$$R_1 = \phi_R \quad (3.17)$$

$$R_i = (1 - \phi_R) \frac{\hat{\pi}_E(d_i)}{\sum_{d_i \in \mathcal{A}_j} \hat{\pi}_E(d_i)}, \quad i = 2, \dots, I. \quad (3.18)$$

Compared to Equation 3.15 the adaptive randomisation probability is fixed to  $\phi_R$  at the lowest dose (the control dose) and for all other dose levels in the admissible set  $\mathcal{A}_j$  a scaled randomisation probability is calculated. By fixing the probability for the control dose we guarantee a greater chance of patients being allocated to this dose-level. Although estimates of efficacy at the control dose-level  $\hat{\pi}_E(d_1)$  do not directly impact its associated randomisation probability the efficacy data that generated the estimate is still included in the efficacy modelling and impacts probabilities for the remaining dose-levels. Also, by scaling the remaining probabilities of dose-levels in the admissible set we ensure that those doses with high estimates of efficacy maintain their proportional advantage of selection over the other non-control doses.

Some adjustments were made to the stopping rule for safety. The WT design assess the lower bound of the 95% binomial confidence interval of the lowest dose to determine whether or not the trial should be stopped. However, with the RtC-WT design since the lowest dose is the control it makes little sense to surmise treatment is toxic here since none of the patients on control would have received the experimental treatment. It is also likely the trial would never recommend stopping even if the treatment is toxic since patients on control are likely to experience a toxic event. The RtC-WT design stops for safety by checking for excess toxicity at the second lowest dose-level (the first non control dose-level).

Once the AR phase ends dose-levels are no longer selected by adaptive randomisation. At this point it will be difficult for patients to be recruited to the

control dose since recommended doses will be based on those with the greatest estimates of efficacy. As such it is important to consider the values set for both your randomisation probability for control  $\phi_R$  and the size of the AR phase  $j_R$ . Wages and Tait simply suggest a 50:50 split between both the AR phase and the maximisation phase and show relatively good performance at this level. However, for RtC-WT the AR phase is the main component and more thought should be given here. In the next section we explore multiple combinations to better understand how these choices impact the operating characteristics of the design. We also compare RtC-WT to the two alternative designs mentioned in section 3.3.1 via simulations and the inspection of operating characteristics specifically, selection probability of the OBD and patient allocation numbers at each dose-level.

## 3.4 Evaluation and Exploration of the Extension via Simulations

In this section we evaluate the performance of RtC-WT in comparison to the two alternative designs mentioned in Section 3.3.1. We also explore the impact of changing the probability of randomisation to control and the number of patients included in the adaptive randomisation phase. These will both be assessed via simulation and inspection of their operating characteristics. To facilitate simulations a generic trial example will be utilised along with a variety of scenarios.

### 3.4.1 Design Specification

Here we detail the design specifications for RtC-WT that we will be using throughout this section. We assume five dose-levels, where the lowest dose is

considered to be the control dose-level. The maximum sample size of the trial is set at 60 with patients recruited in cohorts of three and the first cohort starting at dose-level two (the first treatment dose-level). The pre-specified toxicity upper bound and efficacy lower bound are set at  $\phi_T = 0.35$  and  $\phi_E = 0.15$  respectively. Toxicity and efficacy skeletons are presented in table 3.1. In terms of efficacy-relationships monotonic, unimodal and plateau skeletons were all used. We assume that each of the seven efficacy skeletons are equally likely and set  $v(k) = \frac{1}{7}$ .

TABLE 3.1: Toxicity and Efficacy skeletons for RtC-WT in the example trial.

Skeleton	Dose-levels				
	1	2	3	4	5
$p_i$	0.01	0.1	0.2	0.3	0.4
$q_{i1}$	0.01	0.4	0.3	0.2	0.1
$q_{i2}$	0.01	0.3	0.4	0.3	0.2
$q_{i3}$	0.01	0.2	0.3	0.4	0.3
$q_{i4}$	0.01	0.1	0.2	0.3	0.4
$q_{i5}$	0.01	0.2	0.3	0.4	0.4
$q_{i6}$	0.01	0.3	0.4	0.4	0.4
$q_{i7}$	0.01	0.4	0.4	0.4	0.4

For the control dose we have set our prior beliefs to be very low for both toxicity and efficacy. This can of course be adapted if there is reason to believe that the control dose may be slightly more effective or toxic. Wages and Tait recommend  $(2I - 1)$  efficacy skeletons be used which in this example would be nine, however we have only considered seven. Since we don't expect many efficacy events from our lowest dose we dismiss the two extra efficacy skeletons as the dose-efficacy relationship they represent would be unlikely to occur. For completeness the first extra skeleton would be unimodal with the highest efficacy occurring at dose-level one and the second skeleton would be a plateau relationship with the plateau beginning at dose-level one as well. As with the

values we've used for control these additional skeletons can also be incorporated if there is reason to believe so.

We also include the same stopping rules for safety and futility with the safety rule assessing toxicity at dose-level two. A rule will also be implemented to prevent the skipping of untried doses when escalating. This rule does not apply when de-escalating.

The two parameters we have left to specify are the fixed adaptive randomisation probability for control  $\phi_R$  and the number of patients included in the adaptive randomisation phase  $j_R$ . In Section 3.3.2 we briefly discuss the importance of giving thought when setting these values. This is due to the fact they are the main things driving how RtC-WT works comparatively to the WT design. For example one could set the AR phase to last for the whole trial and keep a relative low probability to randomise to control. Alternatively, the AR phase can be set for half the patients in the trial and double the probability of randomisation could be used. These two approaches could allocate the same number of patients in the control arm but have differing operating characteristics. It could be hypothesised that by setting the AR phase for the whole trial you miss out on the maximisation phase where patients are allocated to the estimated most efficacious dose which could yield slightly worse operating characteristics. We explore different combinations of these parameters in the next section.

### 3.4.2 Impact of AR phase size and probability of randomisation to control on RtC-WT

The impact of the probability of control to randomisation is fairly intuitive as  $\phi_R$  increases the number of patients allocated in the control dose-level is likely to increase. However, this is only in isolation without considering

the size of the AR phase. Increasing the AR phase would also mean more patients are likely allocated to the control dose-level since the randomisation only occurs in the AR phase. The interest lies within the interaction of both of these components and their impacts on operating characteristics. In order to gain a better understanding of this impact on RtC-WT we consider multiple of their possible combinations.

We look at two different probabilities for randomisation to control,  $\phi_R = 0.2$  and  $\phi_R = 0.4$  i.e. 20% and 40% probability of patients being allocated to the control dose-level during the AR phase of the trial. We also consider varying AR phase sizes, specifically  $j_R = 0, 15, 30, 45, 60$  essentially looking at when the AR phase lasts 0%, 25%, 50%, 75% and 100% of the trial. The inclusion of setting the AR phase as 0 is somewhat counter-intuitive since the trial will just be run using the maximisation phase where the most efficacious doses are allocated. As such it is unlikely that the control dose-level would ever be the most efficacious specifically in our scenario here. However its inclusion will serve as a benchmark as the design most likely to achieve optimal performance in terms of locating the OBD since there will be no randomisation and the most efficacious dose will always be the one being tested. Although, many more combinations could be explored this set of 10 provide a good basis for us to gain a better understanding of how RtC-WT works. It also helps us understand how best to optimise RtC-WT for comparisons with alternative designs later on.

To compare these different combinations we use simulations covering a wide range of scenarios. For each scenario we simulate 10000 trials each consisting of 60 patients recruited in cohorts of three. Patient outcomes for toxicity and efficacy are randomly sampled using true toxicity and true efficacy probabilities, these are assumed to be independent of each other. Dose-allocation

decisions are made after each cohort of patients is simulated and then the subsequent cohort is allocated the recommended dose or the trial is stopped when recruitment is reached and if stopping rules are triggered. The rest of the design specification is as defined in Section 3.4.1.

These true toxicity and efficacy probabilities are manipulated to produce each scenario. Scenario 1 to 4 look at monotonically increasing efficacy and toxicity curves. Scenarios 1 and 2 consider effective doses whereas scenarios 3 and 4 concern ineffective doses. Similarly, scenarios 1 and 3 contain all tolerable doses whereas 2 and 4 doses are considered too toxic. Scenarios 5 to 8 show plateau efficacy curves with 5 and 6 plateauing at dose level three and 7 and 8 plateauing at dose level four. Scenarios 6 and 8 doses are also considered too toxic, whereas 5 and 7 are tolerable. Scenarios 9 to 12 show unimodal efficacy curves with 9 and 10 peaking at dose level three and 11 and 12 peaking at four. Scenarios 9 and 11 consider tolerable doses and 10 and 12 are toxic. Operating characteristics and the scenarios under investigation are given in Tables 3.2 and 3.3. The selection probabilities of each combination under each scenario are also given in Table 3.2. The mean number of patients recruited to each dose-level for each scenario and combination is provided in Table 3.3.

For scenario 1 it is relatively simple to select an admissible dose since all doses are tolerable and efficacy increases monotonically. The difficulty is locating the OBD. All of these combinations fail to identify the OBD (dose-level 5) more than 30% of the time. As the size of the AR phase increases from 15 to 60 so do the selection probabilities, going from 17% to 29% and 16% to 22% for randomisation probabilities of 0.2 and 0.33 respectively. Overall, the designs with higher probability of randomising to control fair slightly worse. In the case of no AR phase,  $j_R = 0$ , the design is roughly selects all active doses (dose-levels 2 to 5) at a similar rate, slightly preferring the lower dose levels. It should be noted that the two designs with no AR phase are identical since the

TABLE 3.2: Selection probabilities for multiple combinations of AR phase size and probabilities for randomisation to control.

Scenario	$\phi_R$	$j_R$	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Stop	Scenario	$\phi_R$	$j_R$	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Stop
P(tox)			0.01	0.05	0.1	0.2	0.25		P(tox)			0.01	0.05	0.1	0.2	0.25	
P(eff)			0.01	0.25	0.35	0.45	0.55		P(eff)			0.01	0.25	0.35	0.55	0.55	
1	0.2	0	0	0.28	0.28	0.21	0.23	0	7	0.2	0	0	0.28	0.2	0.3	0.22	0
	0.2	15	0	0.25	0.3	0.27	0.17	0		0.2	15	0	0.23	0.23	0.39	0.16	0
	0.2	30	0	0.18	0.28	0.34	0.21	0		0.2	30	0	0.14	0.18	0.5	0.18	0
	0.2	45	0	0.15	0.24	0.37	0.24	0		0.2	45	0	0.1	0.15	0.55	0.2	0
	0.2	60	0	0.15	0.2	0.36	0.29	0		0.2	60	0	0.09	0.13	0.51	0.26	0
	0.33	0	0	0.28	0.28	0.21	0.23	0		0.33	0	0	0.28	0.2	0.3	0.22	0
	0.33	15	0	0.26	0.33	0.25	0.16	0		0.33	15	0	0.25	0.25	0.36	0.13	0
	0.33	30	0	0.2	0.3	0.33	0.17	0		0.33	30	0	0.16	0.21	0.48	0.14	0
	0.33	45	0	0.16	0.27	0.37	0.2	0		0.33	45	0	0.12	0.18	0.53	0.16	0
	0.33	60	0	0.18	0.23	0.38	0.22	0		0.33	60	0	0.14	0.17	0.51	0.19	0
P(tox)			0.01	0.5	0.55	0.65	0.75		P(tox)			0.01	0.5	0.55	0.65	0.75	
P(eff)			0.01	0.25	0.35	0.45	0.55		P(eff)			0.01	0.25	0.35	0.55	0.55	
2	0.2	0	0.07	0.15	0	0	0	0.77	8	0.2	0	0.07	0.15	0	0	0	0.78
	0.2	15	0.07	0.15	0	0	0	0.78		0.2	15	0.07	0.16	0	0	0	0.77
	0.2	30	0.07	0.16	0	0	0	0.78		0.2	30	0.07	0.15	0	0	0	0.78
	0.2	45	0.06	0.18	0	0	0	0.76		0.2	45	0.06	0.18	0	0	0	0.76
	0.2	60	0.08	0.31	0	0	0	0.61		0.2	60	0.08	0.32	0	0	0	0.6
	0.33	0	0.07	0.15	0	0	0	0.77		0.33	0	0.07	0.15	0	0	0	0.78
	0.33	15	0.07	0.16	0	0	0	0.77		0.33	15	0.06	0.16	0	0	0	0.77
	0.33	30	0.06	0.17	0	0	0	0.77		0.33	30	0.06	0.16	0	0	0	0.78
	0.33	45	0.04	0.21	0	0	0	0.74		0.33	45	0.04	0.22	0	0	0	0.74
	0.33	60	0.04	0.38	0.01	0	0	0.57		0.33	60	0.04	0.37	0.01	0	0	0.58
P(tox)			0.01	0.05	0.1	0.2	0.25		P(tox)			0.01	0.05	0.1	0.2	0.25	
P(eff)			0.01	0.03	0.06	0.09	0.12		P(eff)			0.01	0.35	0.55	0.35	0.25	
3	0.2	0	0	0.03	0.12	0.28	0.36	0.21	9	0.2	0	0	0.32	0.58	0.09	0.01	0
	0.2	15	0	0.05	0.15	0.27	0.34	0.19		0.2	15	0	0.24	0.69	0.06	0.01	0
	0.2	30	0	0.08	0.19	0.31	0.31	0.12		0.2	30	0	0.19	0.74	0.06	0.01	0
	0.2	45	0	0.1	0.2	0.33	0.32	0.06		0.2	45	0	0.18	0.75	0.06	0	0
	0.2	60	0	0.13	0.18	0.31	0.37	0		0.2	60	0	0.23	0.7	0.07	0.01	0
	0.33	0	0	0.03	0.12	0.28	0.36	0.21		0.33	0	0	0.32	0.58	0.09	0.01	0
	0.33	15	0	0.05	0.15	0.29	0.34	0.17		0.33	15	0	0.27	0.66	0.06	0.01	0
	0.33	30	0	0.08	0.17	0.32	0.32	0.11		0.33	30	0	0.22	0.72	0.05	0.01	0
	0.33	45	0	0.12	0.19	0.33	0.32	0.05		0.33	45	0	0.22	0.71	0.06	0.01	0
	0.33	60	0	0.14	0.18	0.32	0.36	0		0.33	60	0	0.26	0.66	0.07	0.01	0
P(tox)			0.01	0.5	0.55	0.65	0.75		P(tox)			0.01	0.5	0.55	0.65	0.75	
P(eff)			0.01	0.03	0.06	0.09	0.12		P(eff)			0.01	0.35	0.55	0.35	0.25	
4	0.2	0	0.01	0.03	0	0	0	0.96	10	0.2	0	0.07	0.15	0	0	0	0.78
	0.2	15	0.01	0.03	0	0	0	0.96		0.2	15	0.07	0.16	0	0	0	0.77
	0.2	30	0.01	0.03	0	0	0	0.95		0.2	30	0.07	0.16	0	0	0	0.78
	0.2	45	0.01	0.04	0	0	0	0.94		0.2	45	0.05	0.19	0	0	0	0.76
	0.2	60	0.08	0.32	0	0	0	0.6		0.2	60	0.07	0.31	0	0	0	0.61
	0.33	0	0.01	0.03	0	0	0	0.96		0.33	0	0.07	0.15	0	0	0	0.78
	0.33	15	0.02	0.03	0	0	0	0.95		0.33	15	0.07	0.16	0	0	0	0.77
	0.33	30	0.01	0.04	0	0	0	0.95		0.33	30	0.06	0.17	0	0	0	0.77
	0.33	45	0.01	0.05	0	0	0	0.93		0.33	45	0.04	0.22	0	0	0	0.74
	0.33	60	0.05	0.37	0.01	0	0	0.57		0.33	60	0.04	0.37	0	0	0	0.58
P(tox)			0.01	0.05	0.1	0.2	0.25		P(tox)			0.01	0.05	0.1	0.2	0.25	
P(eff)			0.01	0.35	0.55	0.55	0.55		P(eff)			0.01	0.25	0.35	0.55	0.35	
5	0.2	0	0	0.31	0.44	0.16	0.09	0	11	0.2	0	0	0.29	0.21	0.45	0.05	0
	0.2	15	0	0.21	0.54	0.2	0.05	0		0.2	15	0	0.23	0.23	0.5	0.04	0
	0.2	30	0	0.13	0.53	0.28	0.06	0		0.2	30	0	0.15	0.2	0.62	0.04	0
	0.2	45	0	0.11	0.52	0.31	0.06	0		0.2	45	0	0.11	0.18	0.66	0.04	0
	0.2	60	0	0.15	0.45	0.33	0.08	0		0.2	60	0	0.11	0.17	0.63	0.09	0
	0.33	0	0	0.31	0.44	0.16	0.09	0		0.33	0	0	0.29	0.21	0.45	0.05	0
	0.33	15	0	0.23	0.55	0.17	0.04	0		0.33	15	0	0.26	0.26	0.44	0.04	0
	0.33	30	0	0.16	0.56	0.23	0.05	0		0.33	30	0	0.17	0.23	0.56	0.04	0
	0.33	45	0	0.14	0.55	0.26	0.05	0		0.33	45	0	0.13	0.22	0.6	0.04	0
	0.33	60	0	0.21	0.48	0.26	0.05	0		0.33	60	0	0.15	0.2	0.57	0.08	0
P(tox)			0.01	0.5	0.55	0.65	0.75		P(tox)			0.01	0.5	0.55	0.65	0.75	
P(eff)			0.01	0.35	0.55	0.55	0.55		P(eff)			0.01	0.25	0.35	0.55	0.35	
6	0.2	0	0.07	0.15	0	0	0	0.78	12	0.2	0	0.07	0.15	0	0	0	0.78
	0.2	15	0.07	0.16	0	0	0	0.77		0.2	15	0.07	0.16	0	0	0	0.77
	0.2	30	0.07	0.16	0	0	0	0.77		0.2	30	0.07	0.15	0	0	0	0.78
	0.2	45	0.05	0.19	0	0	0	0.76		0.2	45	0.06	0.18	0	0	0	0.76
	0.2	60	0.07	0.32	0	0	0	0.61		0.2	60	0.08	0.32	0	0	0	0.6
	0.33	0	0.07	0.15	0	0	0	0.78		0.33	0	0.07	0.15	0	0	0	0.78
	0.33	15	0.07	0.16	0	0	0	0.77		0.33	15	0.06	0.16	0	0	0	0.77
	0.33	30	0.06	0.17	0	0	0	0.77		0.33	30	0.06	0.16	0	0	0	0.78
	0.33	45	0.04	0.22	0	0	0	0.74		0.33	45	0.04	0.22	0	0	0	0.74
	0.33	60	0.04	0.37	0.01	0	0	0.58		0.33	60	0.04	0.37	0.01	0	0	0.58



TABLE 3.3: Mean number of patients treated at each dose for multiple combinations of AR phase size and probabilities for randomisation to control.

Scenario	$\phi_R$	$j_R$	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Total	Scenario	$\phi_R$	$j_R$	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Total
P(tox)			0.01	0.05	0.1	0.2	0.25		P(tox)			0.01	0.05	0.1	0.2	0.25	
P(eff)			0.01	0.25	0.35	0.45	0.55		P(eff)			0.01	0.25	0.35	0.55	0.55	
1	0.2	0	0.1	21.1	16.9	11.2	10.7	60	7	0.2	0	0.1	20.9	13.9	14.3	10.8	60
	0.2	15	2.4	18.3	18	13.6	7.6	59.9		0.2	15	2.4	17.1	15.3	17.9	7.2	59.9
	0.2	30	5.5	14.9	16	15.4	8.2	60		0.2	30	5.4	13.9	13.5	19.5	7.7	60
	0.2	45	8.5	14.2	14.7	14.4	8.2	60		0.2	45	8.5	13.4	13.5	16.9	7.7	60
	0.2	60	11.4	14.3	14.4	12.6	7.3	60		0.2	60	11.4	13.9	14.3	12.9	7.5	60
	0.33	0	0.1	21.1	16.9	11.2	10.7	60		0.33	0	0.1	20.9	13.9	14.3	10.8	60
	0.33	15	4	18.4	18.4	12.6	6.6	60		0.33	15	4	18	16	16.1	5.9	60
	0.33	30	9	14.9	15.7	13.9	6.4	59.9		0.33	30	9	13.8	13.7	17.7	5.8	60
	0.33	45	13.9	13.2	13.8	12.7	6.3	59.9		0.33	45	13.9	12.4	12.6	15.1	6	60
0.33	60	19	12.7	12.6	10.4	5.4	60.1	0.33	60	18.9	12.5	12.5	10.6	5.5	60		
P(tox)			0.01	0.5	0.55	0.65	0.75		P(tox)			0.01	0.5	0.55	0.65	0.75	
P(eff)			0.01	0.25	0.35	0.45	0.55		P(eff)			0.01	0.25	0.35	0.55	0.55	
2	0.2	0	15.3	23.2	0.7	0.1	0	39.3	8	0.2	0	15.2	23.1	0.7	0.1	0	39.1
	0.2	15	15.3	22.8	1	0.1	0	39.2		0.2	15	15.3	22.8	1	0.1	0	39.2
	0.2	30	15.5	22.6	1	0.1	0	39.2		0.2	30	15.4	22.4	0.9	0.1	0	38.8
	0.2	45	16.5	23	1	0.1	0	40.6		0.2	45	16.5	22.9	1	0.1	0	40.5
	0.2	60	17.8	22.6	1	0.1	0	41.5		0.2	60	17.9	22.8	1	0.1	0	41.8
	0.33	0	15.3	23.2	0.7	0.1	0	39.3		0.33	0	15.2	23.1	0.7	0.1	0	39.1
	0.33	15	15.5	22.7	1.1	0.1	0	39.4		0.33	15	15.5	22.7	1.2	0.1	0	39.5
	0.33	30	16	22.5	1.4	0.1	0	40		0.33	30	15.9	22.3	1.3	0.1	0	39.6
	0.33	45	17.5	22.2	1.3	0.1	0	41.1		0.33	45	17.3	22.1	1.3	0.1	0	40.8
0.33	60	20	21.4	1.3	0.1	0	42.8	0.33	60	19.9	21.4	1.3	0.1	0	42.7		
P(tox)			0.01	0.05	0.1	0.2	0.25		P(tox)			0.01	0.05	0.1	0.2	0.25	
P(eff)			0.01	0.03	0.06	0.09	0.12		P(eff)			0.01	0.35	0.55	0.35	0.25	
3	0.2	0	0.1	9.7	11.3	17.5	18.9	57.5	9	0.2	0	0.1	26.4	27.1	5.2	1.2	60
	0.2	15	2.4	10.7	12.3	16.2	16.3	57.9		0.2	15	2.4	18.7	32.5	5.4	0.9	59.9
	0.2	30	5.4	11.1	13.7	15.9	12.9	59		0.2	30	5.4	16.6	28.3	7.6	2	59.9
	0.2	45	8.4	11.3	13.6	15.2	11.2	59.7		0.2	45	8.4	16.2	22.3	9.5	3.5	59.9
	0.2	60	11.5	11.1	13.7	14.3	9.4	60		0.2	60	11.5	16.1	15.6	11.6	5.3	60.1
	0.33	0	0.1	9.7	11.3	17.5	18.9	57.5		0.33	0	0.1	26.4	27.1	5.2	1.2	60
	0.33	15	4	10.2	11.8	15.9	16.3	58.2		0.33	15	4	19.6	30.8	4.9	0.8	60.1
	0.33	30	9	10.4	12.2	15.2	12.4	59.2		0.33	30	8.9	16.4	26.6	6.5	1.6	60
	0.33	45	13.8	10.4	12.3	13.6	9.8	59.9		0.33	45	13.9	15.3	20	8.1	2.7	60
0.33	60	19	10	12.1	11.8	7.1	60	0.33	60	19	14.1	13.3	9.6	4	60		
P(tox)			0.01	0.5	0.55	0.65	0.75		P(tox)			0.01	0.5	0.55	0.65	0.75	
P(eff)			0.01	0.03	0.06	0.09	0.12		P(eff)			0.01	0.35	0.55	0.35	0.25	
4	0.2	0	13.3	18.4	1.1	0.2	0	33	10	0.2	0	15.3	23.3	0.5	0	0	39.1
	0.2	15	13.3	18.2	1.3	0.2	0	33		0.2	15	15.2	22.9	1	0.1	0	39.2
	0.2	30	14.2	18.7	1.2	0.1	0	34.2		0.2	30	15.6	22.7	0.9	0.1	0	39.3
	0.2	45	16.2	20.9	1.2	0.2	0	38.5		0.2	45	16.5	23	1	0.1	0	40.6
	0.2	60	18.1	22.8	1.2	0.1	0	42.2		0.2	60	17.9	22.7	0.9	0.1	0	41.6
	0.33	0	13.3	18.4	1.1	0.2	0	33		0.33	0	15.3	23.3	0.5	0	0	39.1
	0.33	15	13.6	18.3	1.5	0.2	0	33.6		0.33	15	15.4	23	1	0.1	0	39.5
	0.33	30	14.8	18.5	1.6	0.2	0	35.1		0.33	30	16	22.5	1.3	0.1	0	39.9
	0.33	45	17.1	19.8	1.5	0.2	0	38.6		0.33	45	17.6	22.4	1.3	0.1	0	41.4
0.33	60	19.9	21	1.5	0.2	0	42.6	0.33	60	19.9	21.5	1.2	0.1	0	42.7		
P(tox)			0.01	0.05	0.1	0.2	0.25		P(tox)			0.01	0.05	0.1	0.2	0.25	
P(eff)			0.01	0.35	0.55	0.55	0.55		P(eff)			0.01	0.25	0.35	0.55	0.35	
5	0.2	0	0.1	26.1	21.7	7.4	4.8	60.1	11	0.2	0	0.1	21.3	14.4	19.5	4.8	60.1
	0.2	15	2.5	17.2	27	10.6	2.7	60		0.2	15	2.4	17.1	15.6	21.4	3.4	59.9
	0.2	30	5.4	14.3	22.6	13.7	4	60		0.2	30	5.4	13.9	14.3	22.4	4	60
	0.2	45	8.5	14.3	18.6	13.4	5.2	60		0.2	45	8.4	13.7	14.1	18.4	5.3	59.9
	0.2	60	11.4	14.9	14.7	12.3	6.6	59.9		0.2	60	11.5	14.3	14.5	12.8	6.8	59.9
	0.33	0	0.1	26.1	21.7	7.4	4.8	60.1		0.33	0	0.1	21.3	14.4	19.5	4.8	60.1
	0.33	15	4	17.8	27	9	2.2	60		0.33	15	4	18.2	16.3	18.5	3	60
	0.33	30	9	14.4	22.5	11.3	2.9	60.1		0.33	30	9	13.9	14.3	19.5	3.3	60
	0.33	45	13.8	13.7	17.5	11.1	3.9	60		0.33	45	13.9	12.9	13	15.9	4.3	60
0.33	60	18.9	13.3	12.7	10	5	59.9	0.33	60	18.9	12.6	12.6	10.6	5.3	60		
P(tox)			0.01	0.5	0.55	0.65	0.75		P(tox)			0.01	0.5	0.55	0.65	0.75	
P(eff)			0.01	0.35	0.55	0.55	0.55		P(eff)			0.01	0.25	0.35	0.55	0.35	
6	0.2	0	15.4	23.3	0.5	0.1	0	39.3	12	0.2	0	15.3	23.1	0.7	0.1	0	39.2
	0.2	15	15.2	22.8	1	0.1	0	39.1		0.2	15	15.3	22.8	1	0.1	0	39.2
	0.2	30	15.6	22.8	1	0.1	0	39.5		0.2	30	15.4	22.4	0.9	0.1	0	38.8
	0.2	45	16.4	23	0.9	0.1	0	40.4		0.2	45	16.5	22.9	1	0.1	0	40.5
	0.2	60	18	22.8	0.9	0.1	0	41.8		0.2	60	17.9	22.8	1	0.1	0	41.8
	0.33	0	15.4	23.3	0.5	0.1	0	39.3		0.33	0	15.3	23.1	0.7	0.1	0	39.2
	0.33	15	15.3	22.9	1	0.1	0	39.3		0.33	15	15.5	22.7	1.2	0.1	0	39.5
	0.33	30	15.9	22.5	1.2	0.1	0	39.7		0.33	30	15.9	22.3	1.3	0.1	0	39.6
	0.33	45	17.7	22.6	1.3	0.1	0	41.7		0.33	45	17.3	22.1	1.3	0.1	0	40.8
0.33	60	19.9	21.5	1.2	0.1	0	42.7	0.33	60	19.9	21.4	1.3	0.1	0	42.7		

randomisation probabilities are never used. In terms of numbers of patients treated we see more patients in the control arm as AR phase size and randomisation probability increase. This is expected since if you increase the amount of time available for cohorts to be randomised or the probability in which that is done so more patients will be recruited to control. By increasing the probability of randomising to control we can also see that less patients are being treated at the optimal dose. Also, the  $\phi_R$  figure does not guarantee that exact percentage of patients in the control dose. On average these values seem to be less than one patient off.

Scenario 2 has no OBD as all treatment doses are considered toxic. For most of the combinations stopping occurs 74-78% of the time. Slightly concerning is the case where the AR phase lasts the whole trial. Here stopping is less frequent at 61% and 57% for doses  $\phi_R = 0.2$  and  $\phi_R = 0.33$  respectively. One reason why this may occur is that early on during the trial it will be difficult to discern the toxic dose-levels with low numbers of patients and since these designs don't activate the maximisation phase they will constantly be allocating patients to control. As such it may be the case that not enough toxicity events are being collected to recommend to stop. Interestingly when you look at the average number of patients allocated to control this is similar across the board, even for the case where no adaptive randomisation is taking place. This probably happens since none of the treatment dose-levels make it into the admissible set. If there is only one dose-level in the admissible set after modelling toxicity the design will automatically allocate to that dose.

In scenario 3, the treatment is tolerable but the treatment effect is weak. Again there is no OBD and the trial should recommend stopping for futility. For designs where  $j_R$  is set to the max sample size, in this case 60, stopping will never occur here. This is due to the fact there is no maximisation phase and consequently the futility stopping rule doesn't come into play. We can

see those with smaller AR phase stop more often although not enough. Most of the time these designs are selecting dose-level 5 as the OBD since its true efficacy rate is somewhat close to the lower bound of efficacy. We can see the majority of patients being allocated to this dose-level as well. Since this dose is not toxic this seems reasonable but ideally it would be preferable if the designs recommended stopping.

Scenario 4 is where the treatment is considered toxic and inefficacious. Compared to scenario 2 we see high probability of stopping (93% - 96%) approximately 20 % higher for all of the combinations except where the size of the AR phase is the same as the whole trial. This will be due to the futility rule stopping the trial in instances where toxicity events aren't occurring but doses are still ineffective.

Scenario 5 looks at a plateau relationship where dose-efficacy stops increasing after dose 3. Except for when the AR phase size is 0 or 60 the OBD is selected more than 50% of the time. When the AR phase lasts the whole trial the design seems to run into the issue where dose levels 3, 4 and 5 are all admissible and equally efficacious as such the probability of randomising between these will be somewhat similar. The designs with no AR phase seem to get stuck at lower dose-levels since there is also some efficacious effect there. For both of these combinations we can see this reflected in the average patient numbers for each dose. Looking at the differences between the randomisation to control probabilities we see a minimal increase, approximately 1% in selection of the OBD for  $\phi_R = 0.33$ . We also see slightly more patients treated at the OBD for lower numbers of  $j_R$ . This is most likely due to there being less randomisation and more allocation based on efficacy data once an initial set of data has been collected.

Scenario 6 looks at a similar efficacy curve as scenario 5 but all doses are toxic. Once again, this behaves similarly to other toxic scenarios 2 and 4 where

stopping occurs well except in the case where adaptive randomisation lasts the whole trial.

Scenario 7 is similar to scenario 5 except the plateau begins at dose 4. Here the selection probabilities for small AR phases(0-15) fall off but increase fo 60 in comparison to scenario 5. For an AR phase size of 0 the design still gets stuck at the lower doses. Now with the plateau at 4 the OBD is one dose-level further away from the starting dose. Thus the designs with small AR phases are unable to randomise enough patients to higher dose levels and get stuck during their maximisation phase. Inversely this improved the performance for  $j_R = 60$  as there is one less dose level with similar efficacy so the design has an easier time locating the OBD via randomisation. Scenario 8 involves the same efficacy relationship as scenario 7 except when all doses are toxic. Here we see similar performance as prior scenarios with toxic doses.

Scenarios 9 and 11 look at unimodal efficacy relationships where the mos efficacious dose is at doses 3 and 4 respectively. Overall, we see much higher selection probabilities in these scenarios with those in 9 being slightly higher than those in 11. Similar to the plateau relationships we see less performance for those designs with  $j_R = 0$  and  $j_R = 60$ . With these scenarios we also see a slight increase in the average number of patients treated at the OBD. The increase in performance may be due to the fact that there is only one dose with a high level of efficacy whereas previous dose had multiple highly efficacious doses to allocate to. The impact of randomisation probabilities appear to be more apparent in scenario 11 where  $\phi_R = 0.33$  designs have slightly lower performance. As with scenario 7 since the OBD is one dose further from the starting dose and more patients are being randomised to control there's less chance to obtain data on those higher doses through the initial randomisation in the AR phase.

Finally, scenarios 10 and 12 look at the versions of scenario 9 and 11 respectively where all doses are toxic. Once again, similar characteristics are observed to other toxic scenarios.

In general these scenarios show us that there are some issues with certain specifications of  $\phi_R$  and  $j_R$  in some of the scenarios presented. Specifically, in the case of stopping for toxicity, having the AR phase being the same as the sample size causes some issues. Also, an AR phase size of 0 does not perform well if the dose-efficacy relationship plateaus. For the randomisation probabilities performance was mostly similar between the two values we chose. Some difficulties were observed for higher probabilities of randomisation when the OBD is further away from the starting dose-level. In terms of patient numbers at the control dose we see on average a similar number, if not slightly lower, to what would be expected i.e. for  $\phi_R = 0.2$  and  $j_R = 45$  you would expect 9 control patients (20% of 45) our simulations yielded about 8.5 on average dependent on scenario.

Based on these simulations it would be best to use an AR phase size between 25% and 75% of the total sample size and a randomisation to control probability that will produce the number of control patients you are interested in. However, it may be beneficial to investigate various values of  $\phi_R$  as there does appear to be some trade-off in terms of performance and the number of patients recruited to the control dose.

### 3.4.3 Comparison of RtC-WT against Alternative Designs

The simulations in the previous section were about exploring the impact of varying the parameters controlling the randomisation in RtC-WT. In this section we investigate two alternative trial approaches which could be used to

achieve the same aims as RtC-WT, that is to conduct a dose-finding study locating the ODB whilst recruiting patients to a control arm. Simulations will be conducted for these two alternatives across a variety of scenarios and operating characteristics will be compared against those for RtC-WT.

The first alternative approach would be just to use a standard Wages and Tait design and include the lowest dose-level as control. We will refer to this approach as the standard Wages and Tait (WT). Technically this design doesn't aim to recruit control patients but by including it as a dose-level there is still a small probability during the AR phase that this occurs. Either way this will be a good comparator for RtC-WT as we will be able to directly compare how our extension impacts performance compared to a traditional Wages and Tait design. Theoretically since the standard Wages and Tait design won't be forced to allocate patients to the control dose-level you would expect more patients too be allocated at the experimental treatment dose-levels leading to more data on efficacy and toxicity relationships making it easier to locate the ODB. The differences in performance between these two designs could be considered as the cost for including a control dose.

The second design is one which uses a two-arm randomised approach. Patients once recruited are randomised to either a control arm or a dose-finding study arm. The dose-finding study-arm will use the method of Wages and Tait to identify a OBD. We will refer to this method as the two-arm approach. One of the benefits of this approach is that it is fairly simplistic. This could be considered as a straight-forward way of including a control arm into complex designs without having to figure out any complicated mathematics. For example, the EffTox design could be used for the dose-finding arm and due to the two-arm approach we now have a cohort of control patients without building that methodology directly into the design. For the dose-finding study any methodology could be used here to locate an OBD, however we selected

WT to provide more comparisons for RtC-WT. Since the randomisation occurs up front a guaranteed number of patients can be expected in the control arm, which may be a desirable characteristic of this design. In terms of comparisons to RtC-WT this design will allow us to see if it is worth including the control patients directly in the dose-finding aspect of the design and if there's any benefit in terms of operating characteristics.

For RtC-WT we will be using the same design specification as detailed in Section 3.4.1. In terms of parameters for the number of patients in the AR phase and the probability of randomising to control these will be set at  $j_R = 45$  and  $\phi_R = 0.2$  respectively. These values were selected based on the work done in the previous section. This combination of parameters seemed to perform consistently across all the scenarios explored. The standard Wages and Tait approach will also be using the same specification except for the fixed probability of randomisation to control.

For the two-arm approach things are slightly different since patients are being randomised first. Looking at the RtC-WT design we have specified a sample size of 60, an AR phase size of 45 and probability of randomising to control at 20%. Here we would expect roughly nine patients to be allocated to the control arm (20% of 45), looking at Table for this combo we see on average we achieve around 8.5 patients at the control dose-level. To mimic this behaviour for the two-arm approach we would need to specify a randomisation ratio upfront. Based on the parameters set for RtC-WT this can be done generally using the formula:

$$1 : \frac{J}{\phi_R j_r} - 1 \quad (3.19)$$

where  $J$  is the maximum sample size. In this scenario this corresponds to a 1:5.67 (3:17) randomisation. So for the two-arm approach we will have 9

patients in control and 51 patients in the dose-finding study.

The specifications for the dose-finding study will be somewhat similar as well. Here there will only be four dose levels (no control dose-level) i.e doses 2-5 in Section 3.4.1. We also adjust the toxicity and efficacy skeletons accordingly in Table 3.1 as well by removing the values from dose-level 1. Since there is no control dose-level in the design we will just be using approximately 50% of the patients in the AR phase, as recommended by Wages and Tait. As there will be 51 patients in the dose-finding study we set the AR phase to 24, slightly less than 50% as we are using cohorts of three and 51 patients can't be evenly split up between the two phases. All other design specifications remain the same such as the stopping rules and the pre-specified toxicity upper bound and lower bound.

To compare these different approaches simulations will be used covering the same scenarios as in section 3.4.2. For each scenario we simulate 10000 trials each using the specifications mentioned above. Table 3.4 contains the results for scenarios 1 to 12 comparing selection probabilities. Table 3.5 presents the results for the same scenarios looking at the average number of patients treated at each dose.

## 3.5 Discussion

## 3.6 Conclusion



TABLE 3.4: Selection probabilities for alternative trial designs.

Scenario	Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Stop	Scenario	Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Stop
P(tox)		0.01	0.05	0.1	0.2	0.25		P(tox)		0.01	0.05	0.1	0.2	0.25	
P(eff)		0.01	0.25	0.35	0.45	0.55		P(eff)		0.01	0.25	0.35	0.55	0.55	
1	RtC-WT	0	0.15	0.24	0.37	0.24	0	7	RtC-WT	0	0.1	0.15	0.55	0.2	0
	WT	0	0.11	0.21	0.36	0.31	0		WT	0	0.07	0.11	0.53	0.29	0
	TwoArm		0.18	0.25	0.32	0.24	0		TwoArm		0.13	0.16	0.47	0.24	0
P(tox)		0.01	0.5	0.55	0.65	0.75		P(tox)		0.01	0.5	0.55	0.65	0.75	
P(eff)		0.01	0.25	0.35	0.45	0.55		P(eff)		0.01	0.25	0.35	0.55	0.55	
2	RtC-WT	0.06	0.18	0	0	0	0.76	8	RtC-WT	0.06	0.18	0	0	0	0.76
	WT	0.07	0.16	0	0	0	0.77		WT	0.07	0.16	0	0	0	0.77
	TwoArm		0.23	0	0	0	0.77		TwoArm		0.23	0	0	0	0.77
P(tox)		0.01	0.05	0.1	0.2	0.25		P(tox)		0.01	0.05	0.1	0.2	0.25	
P(eff)		0.01	0.03	0.06	0.09	0.12		P(eff)		0.01	0.35	0.55	0.35	0.25	
3	RtC-WT	0	0.1	0.2	0.33	0.32	0.06	9	RtC-WT	0	0.18	0.75	0.06	0	0
	WT	0	0.08	0.21	0.33	0.3	0.08		WT	0	0.16	0.79	0.05	0	0
	TwoArm		0.09	0.2	0.3	0.3	0.1		TwoArm		0.19	0.74	0.06	0	0
P(tox)		0.01	0.5	0.55	0.65	0.75		P(tox)		0.01	0.5	0.55	0.65	0.75	
P(eff)		0.01	0.03	0.06	0.09	0.12		P(eff)		0.01	0.25	0.35	0.45	0.55	
4	RtC-WT	0.01	0.04	0	0	0	0.94	10	RtC-WT	0.05	0.19	0	0	0	0.76
	WT	0.02	0.03	0	0	0	0.95		WT	0.06	0.16	0	0	0	0.77
	TwoArm		0.02	0	0	0	0.98		TwoArm		0.23	0	0	0	0.76
P(tox)		0.01	0.05	0.1	0.2	0.25		P(tox)		0.01	0.05	0.1	0.2	0.25	
P(eff)		0.01	0.35	0.55	0.55	0.55		P(eff)		0.01	0.25	0.35	0.55	0.35	
5	RtC-WT	0	0.11	0.52	0.31	0.06	0	11	RtC-WT	0	0.11	0.18	0.66	0.04	0
	WT	0	0.08	0.46	0.35	0.1	0		WT	0	0.09	0.16	0.7	0.05	0
	TwoArm		0.12	0.49	0.3	0.09	0		TwoArm		0.14	0.19	0.62	0.05	0
P(tox)		0.01	0.5	0.55	0.65	0.75		P(tox)		0.01	0.5	0.55	0.65	0.75	
P(eff)		0.01	0.35	0.55	0.55	0.55		P(eff)		0.01	0.25	0.35	0.55	0.35	
6	RtC-WT	0.05	0.19	0	0	0	0.76	12	RtC-WT	0.06	0.18	0	0	0	0.76
	WT	0.06	0.17	0	0	0	0.77		WT	0.07	0.16	0	0	0	0.77
	TwoArm		0.23	0	0	0	0.77		TwoArm		0.23	0	0	0	0.77

TABLE 3.5: Mean number of patients allocated to each dose-level for alternative trial designs.

Scenario	Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Total	Scenario	Design	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Total
P(tox)		0.01	0.05	0.1	0.2	0.25		P(tox)		0.01	0.05	0.1	0.2	0.25	
P(eff)		0.01	0.25	0.35	0.45	0.55		P(eff)		0.01	0.25	0.35	0.55	0.55	
1	RtC-WT	8.5	14.2	14.7	14.4	8.2	60	7	RtC-WT	8.5	13.4	13.5	16.9	7.7	60
	WT	1.3	14.9	16.1	16.3	11.4	60		WT	1.4	14.2	14.7	18.5	11.2	60
	TwoArm		14.2	14.4	13.6	8.8	51		TwoArm		12.7	12.1	17.2	8.9	50.9
P(tox)		0.01	0.5	0.55	0.65	0.75		P(tox)		0.01	0.5	0.55	0.65	0.75	
P(eff)		0.01	0.25	0.35	0.45	0.55		P(eff)		0.01	0.25	0.35	0.55	0.55	
2	RtC-WT	16.5	23	1	0.1	0	40.6	8	RtC-WT	16.5	22.9	1	0.1	0	40.5
	WT	15.8	23.4	0.9	0.1	0	40.2		WT	15.8	23.3	0.9	0.1	0	40.1
	TwoArm		27	0.7	0.1	0	27.8		TwoArm		27	0.7	0.1	0	27.8
P(tox)		0.01	0.05	0.1	0.2	0.25		P(tox)		0.01	0.05	0.1	0.2	0.25	
P(eff)		0.01	0.03	0.06	0.09	0.12		P(eff)		0.01	0.35	0.55	0.35	0.25	
3	RtC-WT	8.4	11.3	13.6	15.2	11.2	59.7	9	RtC-WT	8.4	16.2	22.3	9.5	3.5	59.9
	WT	0.5	12.2	15.9	17.9	13	59.5		WT	1.4	17.5	25	11.4	4.7	60
	TwoArm		10.6	13.2	14.8	11.7	50.3		TwoArm		15.6	26	7.5	1.9	51
P(tox)		0.01	0.5	0.55	0.65	0.75		P(tox)		0.01	0.5	0.55	0.65	0.75	
P(eff)		0.01	0.03	0.06	0.09	0.12		P(eff)		0.01	0.25	0.35	0.45	0.55	
4	RtC-WT	16.2	20.9	1.2	0.2	0	38.5	10	RtC-WT	16.5	23	1	0.1	0	40.6
	WT	15.6	21.4	1	0.1	0	38.1		WT	15.8	23.2	0.8	0.1	0	39.9
	TwoArm		21.1	0.9	0.1	0	22.1		TwoArm		27.1	0.7	0.1	0	27.9
P(tox)		0.01	0.05	0.1	0.2	0.25		P(tox)		0.01	0.05	0.1	0.2	0.25	
P(eff)		0.01	0.35	0.55	0.55	0.55		P(eff)		0.01	0.25	0.35	0.55	0.35	
5	RtC-WT	8.5	14.3	18.6	13.4	5.2	60	11	RtC-WT	8.4	13.7	14.1	18.4	5.3	59.9
	WT	1.8	15.1	19.4	15.9	7.7	59.9		WT	1.2	14.7	15.7	21.1	7.3	60
	TwoArm		13.2	19.7	13.4	4.7	51		TwoArm		13	13.1	20.4	4.5	51
P(tox)		0.01	0.5	0.55	0.65	0.75		P(tox)		0.01	0.5	0.55	0.65	0.75	
P(eff)		0.01	0.35	0.55	0.55	0.55		P(eff)		0.01	0.25	0.35	0.55	0.35	
6	RtC-WT	16.4	23	0.9	0.1	0	40.4	12	RtC-WT	16.5	22.9	1	0.1	0	40.5
	WT	15.7	23.1	0.8	0.1	0	39.7		WT	15.8	23.3	0.9	0.1	0	40.1
	TwoArm		27.1	0.7	0.1	0	27.9		TwoArm		27	0.7	0.1	0	27.8



# Bibliography

- [1] N. Stransky, A. M. Egloff, A. D. Tward, *et al.*, “The Mutational Landscape of Head and Neck Squamous Cell Carcinoma,” *Science (New York, N.Y.)*, vol. 333, no. 6046, pp. 1157–1160, Aug. 26, 2011, ISSN: 0036-8075. DOI: 10.1126/science.1208130. pmid: 21798893. [Online]. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3415217/>.
- [2] Cancer Research UK. (). “Head and neck cancers statistics,” Cancer Research UK, [Online]. Available: <https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/head-and-neck-cancers>.
- [3] C. E. Round, M. V. Williams, T. Mee, *et al.*, “Radiotherapy Demand and Activity in England 2006–2020,” *Clinical Oncology*, vol. 25, no. 9, pp. 522–530, Sep. 1, 2013, ISSN: 0936-6555. DOI: 10.1016/j.clon.2013.05.005. [Online]. Available: <http://www.sciencedirect.com/science/article/pii/S0936655513002343>.
- [4] D. M. Cignetti, R. S. Weber, and S. Y. Lai, “Head and Neck Cancer: An Evolving Treatment Paradigm,” *Cancer*, vol. 113, pp. 1911–1932, 7 Oct. 1, 2008, ISSN: 0008-543X. DOI: 10.1002/cncr.23654. pmid: 18798532. [Online]. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2751600/>.
- [5] J. Pignon, J. Bourhis, C. Domenge, *et al.*, “Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: Three

- meta-analyses of updated individual data," *The Lancet*, vol. 355, no. 9208, pp. 949–955, Mar. 18, 2000, ISSN: 0140-6736. DOI: 10.1016/S0140-6736(00)90011-4. [Online]. Available: <http://www.sciencedirect.com/science/article/pii/S0140673600900114>.
- [6] M. J. O'Connor, "Targeting the DNA Damage Response in Cancer," *Molecular Cell*, vol. 60, no. 4, pp. 547–560, Nov. 19, 2015, ISSN: 1097-2765. DOI: 10.1016/j.molcel.2015.10.040. [Online]. Available: <http://www.sciencedirect.com/science/article/pii/S109727651500831X>.
- [7] A. Chalmers, "Science in Focus: Combining Radiotherapy with Inhibitors of the DNA Damage Response," *Clinical Oncology*, vol. 28, no. 5, pp. 279–282, May 2016, ISSN: 09366555. DOI: 10.1016/j.clon.2016.01.035. [Online]. Available: <https://linkinghub.elsevier.com/retrieve/pii/S0936655516000649>.
- [8] L. Mei, J. Zhang, K. He, *et al.*, "Ataxia telangiectasia and Rad3-related inhibitors and cancer therapy: Where we stand," *Journal of Hematology & Oncology*, vol. 12, no. 1, p. 43, Apr. 24, 2019, ISSN: 1756-8722. DOI: 10.1186/s13045-019-0733-6. [Online]. Available: <https://doi.org/10.1186/s13045-019-0733-6>.
- [9] C. Le Tourneau, J. J. Lee, and L. L. Siu, "Dose Escalation Methods in Phase I Cancer Clinical Trials," *JNCI: Journal of the National Cancer Institute*, vol. 101, no. 10, pp. 708–720, May 20, 2009, ISSN: 0027-8874. DOI: 10.1093/jnci/djp079. [Online]. Available: <https://academic.oup.com/jnci/article/101/10/708/969691>.
- [10] J. O'Quigley, M. Pepe, and L. Fisher, "Continual Reassessment Method: A Practical Design for Phase 1 Clinical Trials in Cancer," *Biometrics*, vol. 46, no. 1, pp. 33–48, 1990, ISSN: 0006-341X. DOI: 10.2307/2531628. JSTOR: 2531628.

- [11] A. Rogatko, D. Schoeneck, W. Jonas, *et al.*, "Translation of Innovative Designs Into Phase I Trials," *Journal of Clinical Oncology*, vol. 25, no. 31, pp. 4982–4986, Nov. 1, 2007, ISSN: 0732-183X. DOI: [10.1200/JCO.2007.12.1012](https://doi.org/10.1200/JCO.2007.12.1012). [Online]. Available: <https://ascopubs.org/doi/full/10.1200/JCO.2007.12.1012>.
- [12] C. Chiuзан, J. Shtaynberger, G. A. Manji, *et al.*, "Dose-finding designs for trials of molecularly targeted agents and immunotherapies," *Journal of Biopharmaceutical Statistics*, vol. 27, no. 3, pp. 477–494, May 4, 2017, ISSN: 1054-3406. DOI: [10.1080/10543406.2017.1289952](https://doi.org/10.1080/10543406.2017.1289952). pmid: 28166468. [Online]. Available: <https://doi.org/10.1080/10543406.2017.1289952>.
- [13] K. Brock, V. Homer, G. Soul, *et al.*, "Is more better? An analysis of toxicity and response outcomes from dose-finding clinical trials in cancer," *medRxiv*, p. 2020.08.18.20177212, Aug. 21, 2020. DOI: [10.1101/2020.08.18.20177212](https://doi.org/10.1101/2020.08.18.20177212). [Online]. Available: <https://www.medrxiv.org/content/10.1101/2020.08.18.20177212v1>.
- [14] Y. K. Cheung and R. Chappell, "Sequential Designs for Phase I Clinical Trials with Late-Onset Toxicities," *Biometrics*, vol. 56, no. 4, pp. 1177–1182, 2000, ISSN: 1541-0420. DOI: [10.1111/j.0006-341X.2000.01177.x](https://doi.org/10.1111/j.0006-341X.2000.01177.x). [Online]. Available: <https://onlinelibrary.wiley.com/doi/abs/10.1111/j.0006-341X.2000.01177.x>.
- [15] P. F. Thall, R. E. Millikan, P. Mueller, *et al.*, "Dose-Finding with Two Agents in Phase I Oncology Trials," *Biometrics*, vol. 59, no. 3, pp. 487–496, 2003, ISSN: 1541-0420. DOI: [10.1111/1541-0420.00058](https://doi.org/10.1111/1541-0420.00058). [Online]. Available: <https://onlinelibrary.wiley.com/doi/abs/10.1111/1541-0420.00058>.
- [16] G. Yin and Y. Yuan, "Bayesian dose finding in oncology for drug combinations by copula regression," *Journal of the Royal Statistical Society:*

- Series C (Applied Statistics)*, vol. 58, no. 2, pp. 211–224, 2009, ISSN: 1467-9876. DOI: [10.1111/j.1467-9876.2009.00649.x](https://doi.org/10.1111/j.1467-9876.2009.00649.x). [Online]. Available: <https://rss.onlinelibrary.wiley.com/doi/abs/10.1111/j.1467-9876.2009.00649.x>.
- [17] N. A. Wages, M. R. Conaway, and J. O’Quigley, “Continual reassessment method for partial ordering,” *Biometrics*, vol. 67, no. 4, pp. 1555–1563, Dec. 2011, ISSN: 1541-0420. DOI: [10.1111/j.1541-0420.2011.01560.x](https://doi.org/10.1111/j.1541-0420.2011.01560.x). pmid: [21361888](https://pubmed.ncbi.nlm.nih.gov/21361888/).
- [18] —, “Using the time-to-event continual reassessment method in the presence of partial orders,” *Statistics in Medicine*, vol. 32, no. 1, pp. 131–141, Jan. 15, 2013, ISSN: 1097-0258. DOI: [10.1002/sim.5491](https://doi.org/10.1002/sim.5491). pmid: [22806898](https://pubmed.ncbi.nlm.nih.gov/22806898/).
- [19] S. Liu, G. Yin, and Y. Yuan, “BAYESIAN DATA AUGMENTATION DOSE FINDING WITH CONTINUAL REASSESSMENT METHOD AND DELAYED TOXICITY,” *The annals of applied statistics*, vol. 7, no. 4, pp. 1837–2457, Dec. 1, 2013, ISSN: 1932-6157. DOI: [10.1214/13-AOAS661](https://doi.org/10.1214/13-AOAS661). pmid: [24707327](https://pubmed.ncbi.nlm.nih.gov/24707327/). [Online]. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3972824/>.
- [20] G. M. Wheeler, M. J. Sweeting, and A. P. Mander, “A Bayesian model-free approach to combination therapy phase I trials using censored time-to-toxicity data,” *Journal of the Royal Statistical Society. Series C, Applied statistics*, vol. 68, no. 2, pp. 309–329, Feb. 2019, ISSN: 0035-9254. DOI: [10.1111/rssc.12323](https://doi.org/10.1111/rssc.12323). pmid: [30880843](https://pubmed.ncbi.nlm.nih.gov/30880843/). [Online]. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6420054/>.
- [21] N. A. Wages and M. R. Conaway, “Specifications of a continual reassessment method design for phase I trials of combined drugs,” *Pharmaceutical statistics*, vol. 12, no. 4, 2013, ISSN: 1539-1604. DOI: [10.1002/pst.1575](https://doi.org/10.1002/pst.1575).

- pmid: 23729323. [Online]. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3771354/>.
- [22] N. A. Wages and N. Varhegyi, "Pocrm: An R-package for phase I trials of combinations of agents," *Computer Methods and Programs in Biomedicine*, vol. 112, no. 1, pp. 211–218, Oct. 2013, ISSN: 1872-7565. DOI: [10.1016/j.cmpb.2013.05.020](https://doi.org/10.1016/j.cmpb.2013.05.020). pmid: 23871691.
- [23] N. A. Wages, *Pocrm: Dose Finding in Drug Combination Phase I Trials Using PO-CRM*, version 0.12, Mar. 15, 2019. [Online]. Available: <https://CRAN.R-project.org/package=pocrm>.
- [24] N. A. Wages, A. Ivanova, and O. Marchenko, "Practical designs for phase I combination studies in oncology," *Journal of biopharmaceutical statistics*, vol. 26, no. 1, pp. 150–166, 2016, ISSN: 1054-3406. DOI: [10.1080/10543406.2015.1092029](https://doi.org/10.1080/10543406.2015.1092029). pmid: 26379085. [Online]. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4720553/>.
- [25] P. Lesueur, J. Lequesne, J.-M. Grellard, *et al.*, "Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable or partially resectable glioblastoma: OLA-TMZ-RTE-01 trial protocol," *BMC Cancer*, vol. 19, Mar. 4, 2019, ISSN: 1471-2407. DOI: [10.1186/s12885-019-5413-y](https://doi.org/10.1186/s12885-019-5413-y). pmid: 30832617. [Online]. Available: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6399862/>.
- [26] B. Huang and P. F. Kuan, "Time-to-event continual reassessment method incorporating treatment cycle information with application to an oncology phase I trial," *Biometrical Journal. Biometrische Zeitschrift*, vol. 56, no. 6, pp. 933–946, Nov. 2014, ISSN: 1521-4036. DOI: [10.1002/bimj.201300261](https://doi.org/10.1002/bimj.201300261). pmid: 24895140.

- [27] K. Cheung, *Dfcrm: Dose-Finding by the Continual Reassessment Method*, version 0.2-2.1, Jan. 26, 2019. [Online]. Available: <https://CRAN.R-project.org/package=dfcrm>.
- [28] J. O'Quigley and L. Z. Shen, "Continual Reassessment Method: A Likelihood Approach," *Biometrics*, vol. 52, no. 2, pp. 673–684, 1996, ISSN: 0006-341X. DOI: [10.2307/2532905](https://doi.org/10.2307/2532905). JSTOR: [2532905](https://www.jstor.org/stable/2532905).
- [29] C. Ahn, S.-H. Kang, Y. Xie, *et al.*, "Optimal Biological Dose for Molecularly Targeted Therapies," in *Wiley StatsRef: Statistics Reference Online*, American Cancer Society, 2016, pp. 1–12, ISBN: 978-1-118-44511-2. DOI: [10.1002/9781118445112.stat07078.pub2](https://doi.org/10.1002/9781118445112.stat07078.pub2). [Online]. Available: <https://onlinelibrary.wiley.com/doi/abs/10.1002/9781118445112.stat07078.pub2>.
- [30] T. M. Braun, "The bivariate continual reassessment method: Extending the CRM to phase I trials of two competing outcomes," *Controlled Clinical Trials*, vol. 23, no. 3, pp. 240–256, Jun. 1, 2002, ISSN: 0197-2456. DOI: [10.1016/S0197-2456\(01\)00205-7](https://doi.org/10.1016/S0197-2456(01)00205-7). [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S0197245601002057>.
- [31] P. F. Thall and J. D. Cook, "Dose-finding based on efficacy-toxicity trade-offs," *Biometrics*, vol. 60, no. 3, pp. 684–693, Sep. 2004, ISSN: 0006-341X. DOI: [10.1111/j.0006-341X.2004.00218.x](https://doi.org/10.1111/j.0006-341X.2004.00218.x). pmid: [15339291](https://pubmed.ncbi.nlm.nih.gov/15339291/).
- [32] K. Brock, L. Billingham, M. Copland, *et al.*, "Implementing the EffTox dose-finding design in the Matchpoint trial," *BMC Medical Research Methodology*, vol. 17, no. 1, p. 112, Jul. 20, 2017, ISSN: 1471-2288. DOI: [10.1186/s12874-017-0381-x](https://doi.org/10.1186/s12874-017-0381-x). [Online]. Available: <https://doi.org/10.1186/s12874-017-0381-x>.
- [33] Y. Zhou, J. J. Lee, and Y. Yuan, "A utility-based Bayesian optimal interval (U-BOIN) phase I/II design to identify the optimal biological dose for



- targeted and immune therapies,” *Statistics in Medicine*, vol. 38, no. 28, S5299–S5316, 2019, ISSN: 1097-0258. DOI: [10.1002/sim.8361](https://doi.org/10.1002/sim.8361). [Online]. Available: <https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.8361>.
- [34] W. Zhang, D. J. Sargent, and S. Mandrekhar, “An adaptive dose-finding design incorporating both toxicity and efficacy,” *Statistics in Medicine*, vol. 25, no. 14, pp. 2365–2383, 2006, ISSN: 1097-0258. DOI: [10.1002/sim.2325](https://doi.org/10.1002/sim.2325). [Online]. Available: <https://onlinelibrary.wiley.com/doi/abs/10.1002/sim.2325>.
- [35] R. Ananthakrishnan, S. Green, D. Li, *et al.*, “Extensions of the mTPI and TEQR designs to include non-monotone efficacy in addition to toxicity for optimal dose determination for early phase immunotherapy oncology trials,” *Contemporary Clinical Trials Communications*, vol. 10, pp. 62–76, Jun. 1, 2018, ISSN: 2451-8654. DOI: [10.1016/j.conctc.2018.01.006](https://doi.org/10.1016/j.conctc.2018.01.006). [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S2451865417301734>.
- [36] Y. Ji and S.-J. Wang, “Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3 + 3 Design for Practical Phase I Trials,” *Journal of Clinical Oncology*, vol. 31, no. 14, pp. 1785–1791, May 10, 2013, ISSN: 0732-183X. DOI: [10.1200/JCO.2012.45.7903](https://doi.org/10.1200/JCO.2012.45.7903). [Online]. Available: <https://ascopubs.org/doi/10.1200/JCO.2012.45.7903>.
- [37] M. S. Blanchard and J. A. Longmate, “Toxicity equivalence range design (TEQR): A practical Phase I design,” *Contemporary Clinical Trials*, vol. 32, no. 1, pp. 114–121, Jan. 1, 2011, ISSN: 1551-7144. DOI: [10.1016/j.cct.2010.09.011](https://doi.org/10.1016/j.cct.2010.09.011). [Online]. Available: <https://www.sciencedirect.com/science/article/pii/S1551714410001710>.

- 
- [38] M.-K. Riviere, Y. Yuan, J.-H. Jourdan, *et al.*, "Phase I/II dose-finding design for molecularly targeted agent: Plateau determination using adaptive randomization," *Statistical Methods in Medical Research*, vol. 27, no. 2, pp. 466–479, Feb. 1, 2018, ISSN: 0962-2802. DOI: [10.1177/0962280216631763](https://doi.org/10.1177/0962280216631763). [Online]. Available: <https://doi.org/10.1177/0962280216631763>.
- [39] N. A. Wages and C. Tait, "Seamless Phase I/II Adaptive Design for Oncology Trials of Molecularly Targeted Agents," *Journal of Biopharmaceutical Statistics*, vol. 25, no. 5, pp. 903–920, Sep. 3, 2015, ISSN: 1054-3406. DOI: [10.1080/10543406.2014.920873](https://doi.org/10.1080/10543406.2014.920873). pmid: 24904956. [Online]. Available: <https://doi.org/10.1080/10543406.2014.920873>.
- [40] K. Brock. (Oct. 18, 2020). "Modular Approach to Dose Finding Clinical Trials [R package escalation version 0.1.4]," [Online]. Available: <https://CRAN.R-project.org/package=escalation>.