

# 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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## **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.

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

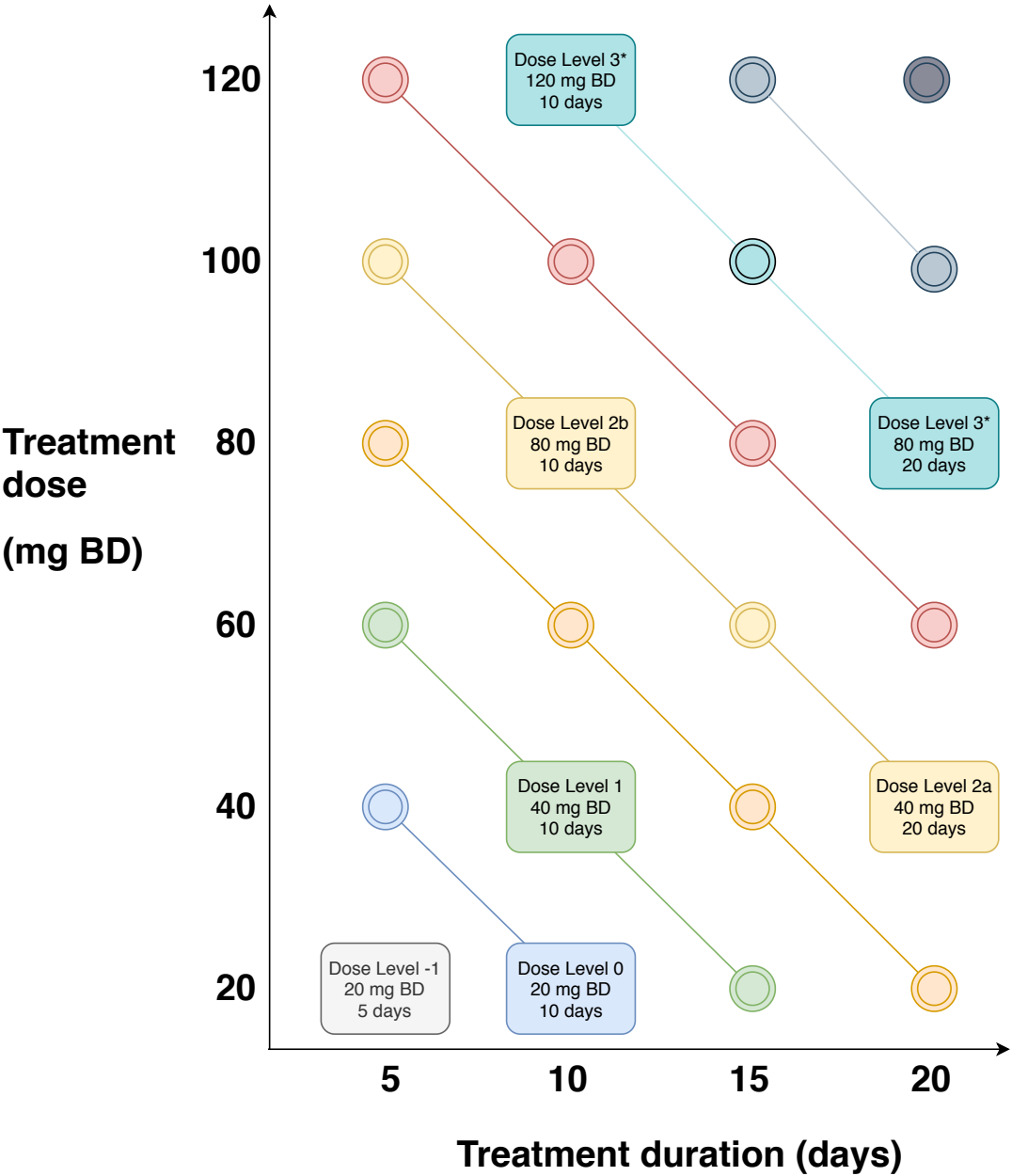
$$2. d_{-1} \rightarrow d_0 \rightarrow d_1 \rightarrow d_{2b} \rightarrow d_{2a} \rightarrow d_3$$

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

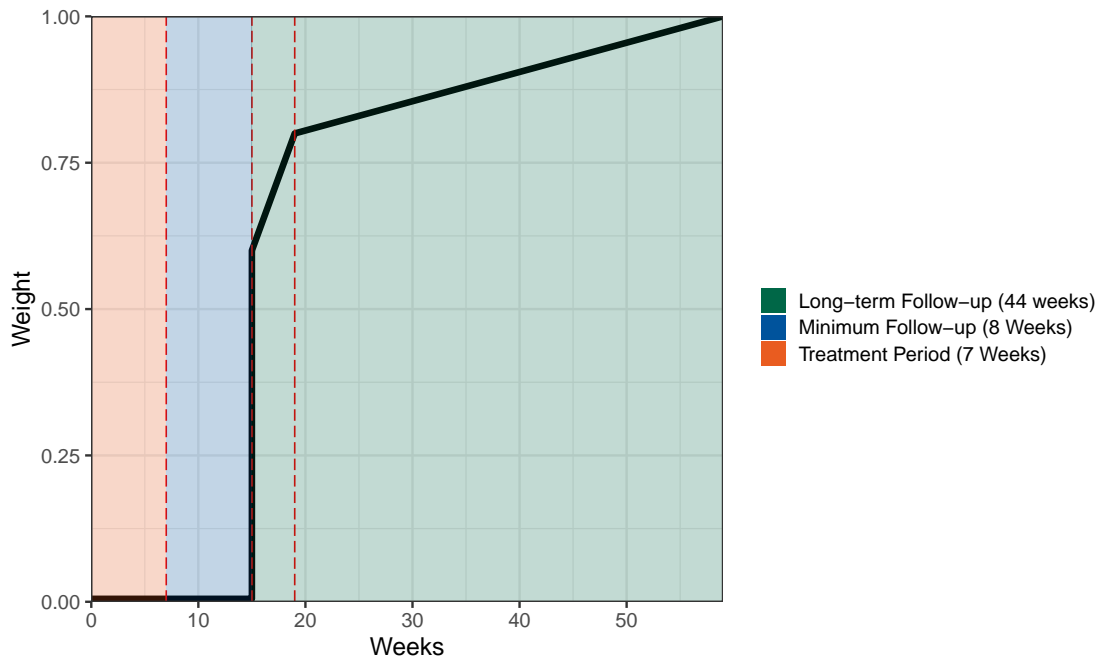
contribution). Linear weighting functions will be employed for any patient with a length of follow up between these three time points. One weight function to calculate weights between 8-12 weeks and another for weights between 12-52 weeks. For the weighting function  $w(u; t_1, t_2, t_3)$  where  $u$  is the time-to-toxicity of patient  $j$  and  $t_1, t_2, t_3$  is the time 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. It is recommended by Morris et al. [29] to detail the Monte Carlo standard error in order to quantify the simulations uncertainty. In the case of a 50% selection probability the Monte Carlo standard error 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	0.08
	P(select)	<b>0.68</b>	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	0.01
	P(select)	0.23	<b>0.51</b>	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	<0.01
	P(select)	0.02	0.2	<b>0.55</b>	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	<0.01
	P(select)	0	0.02	0.22	<b>0.48</b>	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	<b>0.43</b>	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	<b>0.78</b>	
	% 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	<0.01
	P(select)	0	0.03	0.12	0.31	<b>0.28</b>	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	<b>0.74</b>
	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

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	
	P(select)	<b>0.67</b>	0.19	0.05	0	0.01	0	0.08
	% of patients	39	32	20	6	3	0	
	Mean number of patients	10.19	8.43	5.27	1.6	0.68	0.07	
10: TD25 @0	True DLT rate	0.12	0.25	0.4	0.5	0.45	0.55	
	P(select)	0.23	<b>0.52</b>	0.2	0.02	0.02	0	0.01
	% of patients	18	36	29	11	6	1	
	Mean number of patients	5.24	10.64	8.82	3.16	1.85	0.24	
11: TD25 @1	True DLT rate	0.09	0.12	0.25	0.45	0.4	0.5	
	P(select)	0.02	0.2	<b>0.55</b>	0.09	0.14	0.01	<0.01
	% of patients	4	20	34	21	17	3	
	Mean number of patients	1.16	6.43	11.07	6.83	5.6	1.07	
12: TD25 @2a	True DLT rate	0.06	0.09	0.12	0.25	0.15	0.45	
	P(select)	0	0.01	0.08	<b>0.44</b>	0.33	0.14	<0.01
	% of patients	1	11	16	30	24	18	
	Mean number of patients	0.48	3.78	5.24	10.1	7.9	6.07	
13: TD25 @2b	True DLT rate	0.03	0.06	0.09	0.35	0.25	0.4	
	P(select)	0	0	0.15	0.31	<b>0.43</b>	0.11	0
	% of patients	1	11	18	30	28	14	
	Mean number of patients	0.25	3.5	5.9	9.82	9.14	4.54	
14: TD25 @3	True DLT rate	0.01	0.03	0.06	0.12	0.09	0.25	
	P(select)	0	0	0	0.13	0.09	<b>0.78</b>	0
	% of patients	0	10	11	19	16	43	
	Mean number of patients	0.1	3.13	3.51	5.88	5.06	13.13	
15: Equal steps in DLT rate	True DLT rate	0.05	0.1	0.15	0.25	0.2	0.3	
	P(select)	0	0.02	0.12	<b>0.32</b>	0.27	0.26	<0.01
	% of patients	2	13	19	27	22	18	
	Mean number of patients	0.54	4.02	5.93	8.56	6.89	5.75	
16: All toxic	True DLT rate	0.5	0.6	0.65	0.75	0.7	0.8	
	P(select)	0.27	0	0	0	0	0	<b>0.73</b>
	% of patients	56	27	15	2	0	0	
	Mean number of patients	9.01	4.28	2.39	0.38	0.05	0	

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 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.

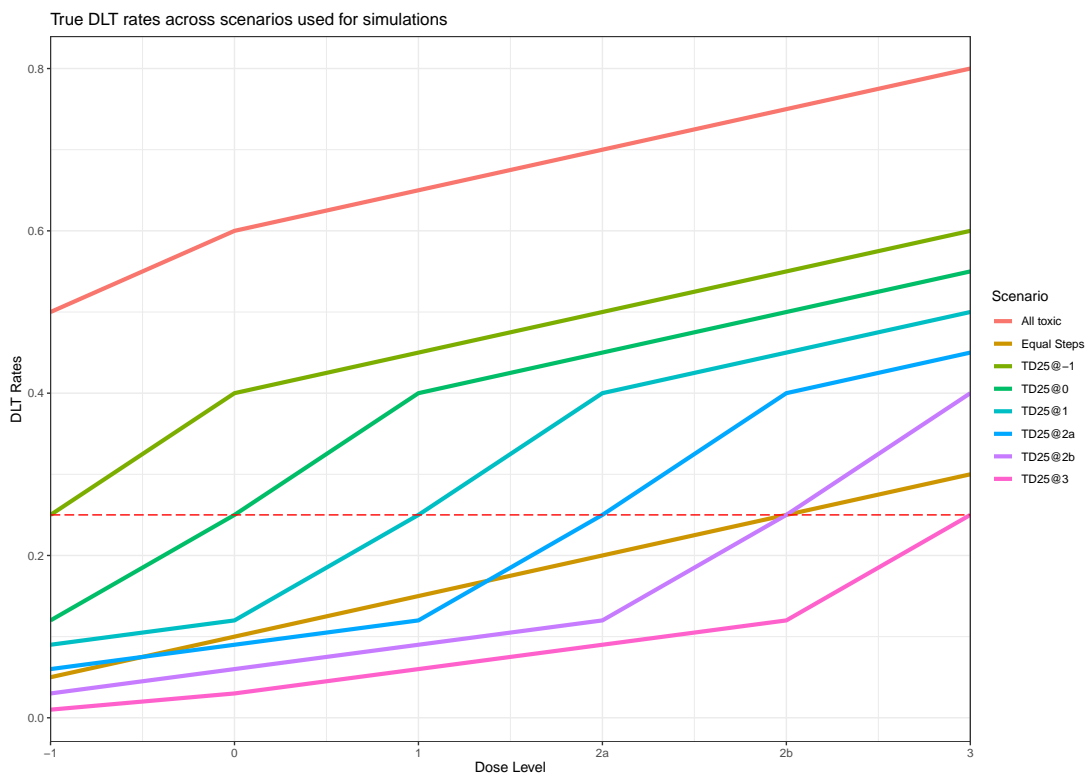
## 2.4 Exploring other designs

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

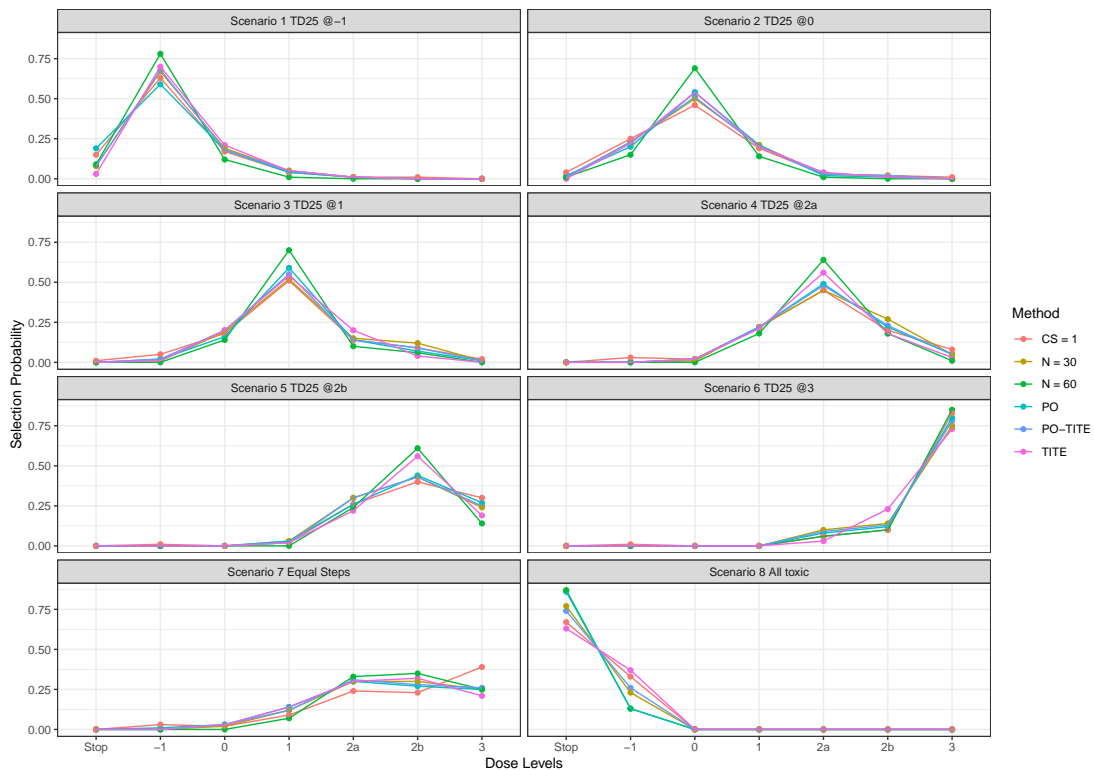
only be made every third patient after a specific amount of time. This is done for safety and practicality reasons but means that some patients may not be able to enter the trial and it also loses some of the benefits of the TITE-CRM. We also have a sample size of 60 patients but include a stopping rule 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 the rate of efficacy increases monotonically with the dose-level and probability of toxicity. 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 that utilises the body's immune system to fight 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 [30]. 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. 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 [31] 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, or 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 [32] 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 [33].

Zhou et al. [34] 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. [35] 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 are then used to identify the OBD similar to the CRM.

Anathakrishnan et al. [36] produced extensions to the modified Toxicity Probability Interval (mTPI) design by Ji & Wang [37] and Toxicity Equivalent Range (TEQR) design by Blanchard & Longmate [38] 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 to the observed response rates or the differences in observed response rates to determine the optimal dose.

Riviere et al. [39] 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 patients to the dose-level closest to the likely plateau point.

This chapter revolves around the seamless phase I/II dose-finding adaptive design by Wages and Tait [40], which 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 been completed we move to the maximisation phase. In this phase, patients are allocated to the dose in the tolerable set which maximises the probability of efficacy.

The incorporation of an AR phase early on into the trial is beneficial since there may be a lack of data 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.

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, we finish with a discussion in Section 3.5.

## 3.2 The Wages and Tait Design

In this section, we detail the Wages and Tait design using the same notation as presented in their paper [40]. 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 an event didn't happen and 1 indicates that it did.

Wages and Tait [40] 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 is required 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 used 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 is considered. They use a class of skeletons that correspond to various dose-efficacy relationships. These relationships might be monotonically increasing (as the dose-levels 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 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/dose-level. 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

Typically, seamless phase I/II trial designs perform the tasks of phase I and phase II trials. However, they do not replace the need for randomised phase II trials entirely where preliminary efficacy data is collected on an experimental treatment versus control to determine the need for a larger phase III study. This

is our main motivation for introducing RtC-WT. By introducing the ability to randomise to control in the Wages and Tait method we can achieve similar objectives to randomised phase II studies.

An example of where this design may be beneficial is in the investigation of a standard of care treatment in combination with an experimental treatment. The standard of care treatment could be included as the control dose and should have a well understood toxicity and efficacy profile which could be incorporated into the toxicity and efficacy skeletons. Further dose levels would also receive standard of care along with increasing levels of the experimental treatment, here the interaction between the two treatments in terms of toxicity and efficacy could be investigated and an OBD could be found using the RtC-WT design.

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 easy implementation of this design in his R package *escalation* [41]. Considering all these factors extensions to this design can be executed without too many obstacles.

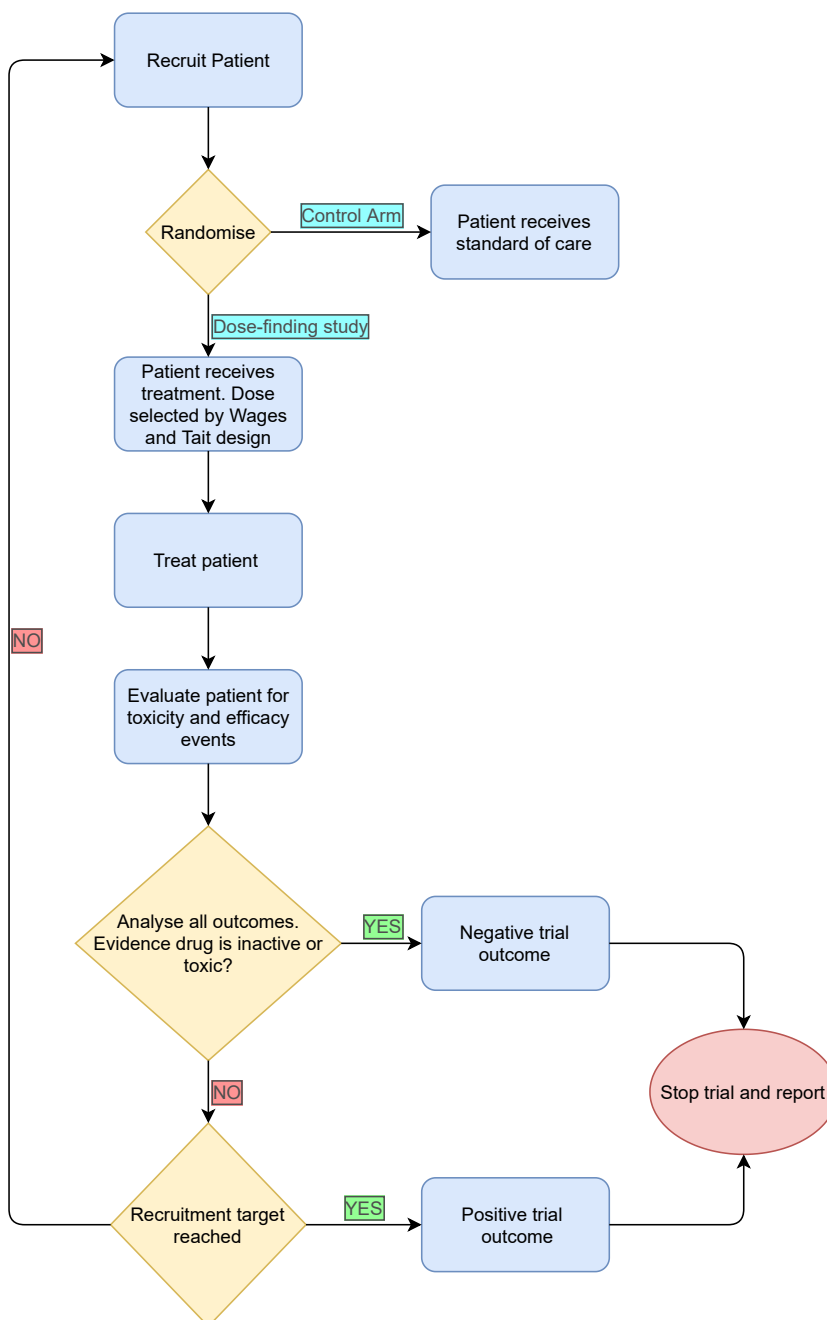
The WT design can be considered fairly unique due to its use of adaptive randomisation. Whilst adaptive randomisation is not the core focus of the design it is still a distinguishing factor that could be leveraged to help investigators answer questions other designs can't. Specifically, the randomisation 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 that 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 a control arm or a dose-finding arm. Those patients allocated in the dose-finding arm will then be a part 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 and 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 are 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.



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



Both of these approaches have their merit but also have flaws as well. RtC-WT is somewhat of a middle ground that 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 their corresponding skeleton values must be 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 assesses 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 unlikely 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 treatment 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, the selection probabilities 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  $\phi_E = 0.50$  respectively. Toxicity and efficacy skeletons,  $p_i$  and  $q_i$  respectively, 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 is equally likely and set  $v(k) = \frac{1}{7}$ .

For the control dose, we have set our prior beliefs for the probability of toxicity at 10% and the probability of efficacy at 30%. This can of course be adjusted

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

Skeleton	Dose-levels				
	1	2	3	4	5
$p_i$	0.1	0.15	0.25	0.35	0.45
$q_{i1}$	0.3	0.7	0.6	0.5	0.4
$q_{i2}$	0.3	0.6	0.7	0.6	0.5
$q_{i3}$	0.3	0.5	0.6	0.7	0.6
$q_{i4}$	0.3	0.4	0.5	0.6	0.7
$q_{i5}$	0.3	0.5	0.6	0.7	0.7
$q_{i6}$	0.3	0.6	0.7	0.7	0.7
$q_{i7}$	0.3	0.7	0.7	0.7	0.7

if there is reason to believe that the control dose may be slightly more/less 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.

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 discussed 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 compared to the standard

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 different 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 effect of adjusting the probability of randomising to control  $\phi_R$  is fairly intuitive, as the probability increase the number of patients allocated to the control dose-level is also 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. To gain a better understanding of this impact on RtC-WT we consider multiple combinations.

We look at two different probabilities for randomisation to control,  $\phi_R = 0.2$  and  $\phi_R = 0.33$  i.e. 20% and 33% 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 estimated most efficacious dose will always be the one being tested. Similarly, by setting the AR phase at 60 we limit some of the designs features by never entering the maximisation phase to select dose levels based on efficacy. Also, the stopping rule for futility doesn't come into play. 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 and then the subsequent cohort is allocated the recommended dose. The trial could also be stopped here if the recruitment target is reached or if any of the stopping rules are triggered. The rest of the design specification is as defined in Section 3.4.1.

The true toxicity and efficacy probabilities are manipulated to produce each scenario for the simulations. Table 3.2 shows a summary of the scenarios that will be used. We look at a combination of five different efficacy curves with three toxicity curves giving 15 scenarios all together. The five dose-efficacy relationships we consider are; monotonically increasing, unimodal (at dose level

3), plateau (starting at dose level 3) , monotonically decreasing and finally no efficacy. For toxicity we look at scenarios where all doses are tolerable, all doses are toxic and a scenario where only higher doses (dose-levels 4 and 5) are toxic. We also list which doses would be considered the OBD under the designs specification along with which doses would be good for each of the scenarios. The OBD in this context would be the dose which maximises efficacy whilst not breaching the toxicity limit. Good doses are those which are considered safe (probability of toxicity  $\leq 35\%$ ) and efficacious (probability of efficacy  $\geq 50\%$ ). For scenarios which are too toxic/lack efficacy we would expect the trial to stop early, here we have labelled the OBD as being the probability of stopping and good doses as the probability of stopping and selecting dose-level 1, the control dose. Whilst allocating patients to dose-level 1 in these scenarios is not necessarily a bad thing it would likely mean more patients are exposed to the toxic/inefficacious doses which is not optimal, hence the distinction.

Operating characteristics for the scenarios under investigation are given in Table 3.3. The table provides the following operating characteristics:

- P(OBD) - Probability of selecting the OBD
- P(Good) - Probability of selecting a good dose
- N(OBD) - Mean number of patients treated at the OBD
- N(Good) - Mean number of patients treated at good doses
- N(Control) - Mean number of patients treated at the control dose (dose-level 1)

These are provided for each scenario under the 10 different parameterisations of  $\phi_R$  and  $j_R$ . For certain scenarios, where the ideal outcome would be to stop early, N(OBD) is left blank as patients aren't allocated to a specific dose.



Also, for these scenarios  $N(\text{Good})$  and  $N(\text{Control})$  are the same as the only good dose patients can be allocated to is the control. Then for scenarios where there is only one good dose-level that would be the OBD as well so  $P(\text{OBD})$  and  $P(\text{Good})$  would be the same as would  $N(\text{OBD})$  and  $N(\text{Good})$ .

TABLE 3.2: Summary of the efficacy and toxicity curves used in each scenario.

Scenario		1	2	3	4	5	Description	ODB	Good Dose
1	tox	0.1	0.2	0.25	0.3	0.35	All doses tolerable	5	3-5
	eff	0.3	0.4	0.5	0.6	0.7	Monotone increasing		
2	tox	0.1	0.45	0.5	0.55	0.6	Too toxic	Stop	Stop/Control
	eff	0.3	0.4	0.5	0.6	0.7	Monotone increasing		
3	tox	0.1	0.25	0.35	0.45	0.55	High doses toxic	3	3
	eff	0.3	0.4	0.5	0.6	0.7	Monotone increasing		
4	tox	0.1	0.2	0.25	0.3	0.35	All doses tolerable	3	3-4
	eff	0.3	0.4	0.7	0.5	0.4	Unimodal		
5	tox	0.1	0.45	0.5	0.55	0.6	Too toxic	Stop	Stop/Control
	eff	0.3	0.4	0.7	0.5	0.4	Unimodal		
6	tox	0.1	0.25	0.35	0.45	0.55	High doses toxic	3	3
	eff	0.3	0.4	0.7	0.5	0.4	Unimodal		
7	tox	0.1	0.2	0.25	0.3	0.35	All doses tolerable	3	3-5
	eff	0.3	0.4	0.6	0.6	0.6	Plateau		
8	tox	0.1	0.45	0.5	0.55	0.6	Too toxic	Stop	Stop/Control
	eff	0.3	0.4	0.6	0.6	0.6	Plateau		
9	tox	0.1	0.25	0.35	0.45	0.55	High doses toxic	3	3
	eff	0.3	0.4	0.6	0.6	0.6	Plateau		
10	tox	0.1	0.2	0.25	0.3	0.35	All doses tolerable	2	2-4
	eff	0.3	0.7	0.6	0.5	0.4	Monotone decreasing		
11	tox	0.1	0.45	0.5	0.55	0.6	Too toxic	Stop	Stop/Control
	eff	0.3	0.7	0.6	0.5	0.4	Monotone decreasing		
12	tox	0.1	0.25	0.35	0.45	0.55	High doses toxic	2	2-3
	eff	0.3	0.7	0.6	0.5	0.4	Monotone decreasing		
13	tox	0.1	0.2	0.25	0.3	0.35	All doses tolerable	Stop	Stop/Control
	eff	0.3	0.3	0.3	0.3	0.3	No Efficacy		
14	tox	0.1	0.45	0.5	0.55	0.6	Too toxic	Stop	Stop/Control
	eff	0.3	0.3	0.3	0.3	0.3	No Efficacy		
15	tox	0.1	0.25	0.35	0.45	0.55	High doses toxic	Stop	Stop/Control
	eff	0.3	0.3	0.3	0.3	0.3	No Efficacy		

TABLE 3.3: Operating characteristics for multiple combinations of AR phase size and probabilities for randomisation to control. Probability of selecting the OBD or good dose levels, mean number of patients treated at those dose levels and at the control dose after 10000 simulations.

Scenario	$\phi_R$	$j_R$	OBD	Good Doses	P(OBD)	P(Good)	N(OBD)	N(Good)	N(Control)
1	0.2	0	5	3-5	0.05	0.60	2.8	32.1	1.2
		15	5	3-5	0.05	0.65	2.7	32	3.6
		30	5	3-5	0.05	0.71	2.2	31.1	6.4
		45	5	3-5	0.05	0.76	1.5	27.5	9.4
		60	5	3-5	0.04	0.80	1.1	22.9	12.4
	0.33	0	5	3-5	0.05	0.60	2.8	32.1	1.2
		15	5	3-5	0.07	0.67	3.1	32.6	4.9
		30	5	3-5	0.06	0.75	2.2	30.4	9.8
		45	5	3-5	0.05	0.79	1.3	25.5	14.7
		60	5	3-5	0.03	0.82	0.8	19.4	19.6
2	0.2	0	stop	stop/1	0.81	0.85	-	10.1	10.1
		15	stop	stop/1	0.80	0.85	-	11	11
		30	stop	stop/1	0.77	0.81	-	13.2	13.2
		45	stop	stop/1	0.72	0.75	-	15.6	15.6
		60	stop	stop/1	0.41	0.50	-	17.9	17.9
	0.33	0	stop	stop/1	0.81	0.85	-	10.1	10.1
		15	stop	stop/1	0.77	0.83	-	11.4	11.4
		30	stop	stop/1	0.75	0.79	-	14	14
		45	stop	stop/1	0.67	0.70	-	17.6	17.6
		60	stop	stop/1	0.38	0.42	-	20.7	20.7
3	0.2	0	3	3	0.25	0.25	15.5	15.5	2.6
		15	3	3	0.31	0.31	16.8	16.8	4.7
		30	3	3	0.35	0.35	16.8	16.8	7.5
		45	3	3	0.42	0.42	15.5	15.5	10.4
		60	3	3	0.48	0.48	12.7	12.7	13.3
	0.33	0	3	3	0.25	0.25	15.5	15.5	2.6
		15	3	3	0.32	0.32	17.2	17.2	5.8
		30	3	3	0.39	0.39	17.3	17.3	10.4
		45	3	3	0.46	0.46	15.2	15.2	15.2
		60	3	3	0.52	0.52	11.5	11.5	20.1

TABLE 3.3: Operating characteristics (continued)

Scenario	$\phi_R$	$j_R$	OBD	Good Doses	P(OBD)	P(Good)	N(OBD)	N(Good)	N(Control)
4	0.2	0	3	3-4	0.69	0.75	32.3	37.2	1.3
		15	3	3-4	0.69	0.76	30.3	35.5	3.5
		30	3	3-4	0.71	0.81	26.4	32.3	6.5
		45	3	3-4	0.73	0.83	21.6	27.4	9.5
		60	3	3-4	0.71	0.83	16	21.7	12.4
	0.33	0	3	3-4	0.69	0.75	32.3	37.2	1.3
		15	3	3-4	0.69	0.77	29.5	35.1	5
		30	3	3-4	0.70	0.81	24.8	31	9.9
		45	3	3-4	0.70	0.84	19.7	25.4	14.7
		60	3	3-4	0.68	0.83	13.7	18.5	19.5
5	0.2	0	stop	stop/1	0.81	0.86	-	10.1	10.1
		15	stop	stop/1	0.79	0.84	-	11.1	11.1
		30	stop	stop/1	0.77	0.82	-	13.1	13.1
		45	stop	stop/1	0.71	0.75	-	15.6	15.6
		60	stop	stop/1	0.41	0.49	-	17.9	17.9
	0.33	0	stop	stop/1	0.81	0.86	-	10.1	10.1
		15	stop	stop/1	0.78	0.83	-	11.3	11.3
		30	stop	stop/1	0.75	0.78	-	14.1	14.1
		45	stop	stop/1	0.67	0.70	-	17.6	17.6
		60	stop	stop/1	0.38	0.43	-	20.8	20.8
6	0.2	0	3	3	0.37	0.37	21.2	21.2	2.6
		15	3	3	0.41	0.41	21.3	21.3	4.5
		30	3	3	0.45	0.45	19.6	19.6	7.5
		45	3	3	0.50	0.50	17.1	17.1	10.4
		60	3	3	0.54	0.54	12.8	12.8	13.4
	0.33	0	3	3	0.37	0.37	21.2	21.2	2.6
		15	3	3	0.42	0.42	21.4	21.4	5.8
		30	3	3	0.50	0.50	20.3	20.3	10.4
		45	3	3	0.55	0.55	16.6	16.6	15.1
		60	3	3	0.59	0.59	11.5	11.5	20.1

TABLE 3.3: Operating characteristics (continued)

Scenario	$\phi_R$	$j_R$	OBD	Good Doses	P(OBD)	P(Good)	N(OBD)	N(Good)	N(Control)
7	0.2	0	3	3-5	0.48	0.70	23.9	35.6	1.3
		15	3	3-5	0.50	0.73	23.7	35	3.5
		30	3	3-5	0.52	0.78	21.8	32.4	6.4
		45	3	3-5	0.56	0.81	19.3	27.9	9.4
		60	3	3-5	0.57	0.82	15.8	22.5	12.5
	0.33	0	3	3-5	0.48	0.70	23.9	35.6	1.3
		15	3	3-5	0.49	0.75	22.7	35.1	5
		30	3	3-5	0.51	0.80	20.8	31.6	9.7
		45	3	3-5	0.55	0.84	17.7	26	14.7
		60	3	3-5	0.56	0.84	13.7	19.6	19.5
8	0.2	0	stop	stop/1	0.81	0.85	-	10.2	10.2
		15	stop	stop/1	0.79	0.84	-	11.1	11.1
		30	stop	stop/1	0.77	0.81	-	13.2	13.2
		45	stop	stop/1	0.71	0.76	-	15.6	15.6
		60	stop	stop/1	0.41	0.50	-	17.9	17.9
	0.33	0	stop	stop/1	0.81	0.85	-	10.2	10.2
		15	stop	stop/1	0.78	0.82	-	11.3	11.3
		30	stop	stop/1	0.75	0.79	-	14	14
		45	stop	stop/1	0.69	0.71	-	17.4	17.4
		60	stop	stop/1	0.38	0.43	-	20.8	20.8
9	0.2	0	3	3	0.34	0.34	18.6	18.6	2.6
		15	3	3	0.36	0.36	19.2	19.2	4.6
		30	3	3	0.42	0.42	18.3	18.3	7.5
		45	3	3	0.45	0.45	16.3	16.3	10.3
		60	3	3	0.50	0.50	12.9	12.9	13.3
	0.33	0	3	3	0.34	0.34	18.6	18.6	2.6
		15	3	3	0.38	0.38	19.7	19.7	5.9
		30	3	3	0.45	0.45	18.6	18.6	10.4
		45	3	3	0.52	0.52	15.9	15.9	15.2
		60	3	3	0.56	0.56	11.5	11.5	20.1

TABLE 3.3: Operating characteristics (continued)

Scenario	$\phi_R$	$j_R$	OBD	Good Doses	P(OBD)	P(Good)	N(OBD)	N(Good)	N(Control)
10	0.2	0	2	2-4	0.77	0.97	45.1	57.1	1.3
		15	2	2-4	0.79	0.97	41.8	55.3	3.5
		30	2	2-4	0.79	0.98	37.2	52.5	6.5
		45	2	2-4	0.79	0.99	32.2	49.6	9.4
		60	2	2-4	0.80	0.99	26.4	46.4	12.3
	0.33	0	2	2-4	0.77	0.97	45.1	57.1	1.3
		15	2	2-4	0.77	0.97	40.1	53.6	5
		30	2	2-4	0.76	0.98	34.6	49.1	9.8
		45	2	2-4	0.76	0.99	28.4	44.3	14.7
		60	2	2-4	0.78	0.99	22.3	39.2	19.6
11	0.2	0	stop	stop/1	0.65	0.74	-	11.7	11.7
		15	stop	stop/1	0.65	0.72	-	12.3	12.3
		30	stop	stop/1	0.62	0.69	-	13.8	13.8
		45	stop	stop/1	0.57	0.63	-	15.7	15.7
		60	stop	stop/1	0.41	0.49	-	17.9	17.9
	0.33	0	stop	stop/1	0.65	0.74	-	11.7	11.7
		15	stop	stop/1	0.64	0.72	-	12.5	12.5
		30	stop	stop/1	0.60	0.67	-	14.7	14.7
		45	stop	stop/1	0.52	0.56	-	17.7	17.7
		60	stop	stop/1	0.38	0.42	-	20.9	20.9
12	0.2	0	2	2-3	0.83	0.92	47.3	53.7	2.7
		15	2	2-3	0.83	0.93	43.6	51.8	4.7
		30	2	2-3	0.82	0.95	39.7	49.3	7.4
		45	2	2-3	0.84	0.96	35.9	46.4	10.4
		60	2	2-3	0.85	0.97	31.7	43.5	13.2
	0.33	0	2	2-3	0.83	0.92	47.3	53.7	2.7
		15	2	2-3	0.81	0.94	41.9	50.7	5.9
		30	2	2-3	0.80	0.95	36.6	46.3	10.4
		45	2	2-3	0.81	0.96	31.7	41.8	15.3
		60	2	2-3	0.82	0.97	26	36.8	20

TABLE 3.3: Operating characteristics (continued)

Scenario	$\phi_R$	$j_R$	OBD	Good Doses	P(OBD)	P(Good)	N(OBD)	N(Good)	N(Control)
13	0.2	0	stop	stop/1	0.82	0.82	-	1.2	1.2
		15	stop	stop/1	0.78	0.78	-	3.5	3.5
		30	stop	stop/1	0.70	0.70	-	6.5	6.5
		45	stop	stop/1	0.57	0.57	-	9.5	9.5
		60	stop	stop/1	0.01	0.01	-	12.4	12.4
	0.33	0	stop	stop/1	0.82	0.82	-	1.2	1.2
		15	stop	stop/1	0.76	0.76	-	4.9	4.9
		30	stop	stop/1	0.68	0.68	-	9.7	9.7
		45	stop	stop/1	0.54	0.54	-	14.7	14.7
		60	stop	stop/1	0.01	0.01	-	19.6	19.6
14	0.2	0	stop	stop/1	0.96	0.97	-	8.3	8.3
		15	stop	stop/1	0.95	0.96	-	9.6	9.6
		30	stop	stop/1	0.94	0.95	-	12.4	12.4
		45	stop	stop/1	0.92	0.93	-	15.5	15.5
		60	stop	stop/1	0.42	0.50	-	17.7	17.7
	0.33	0	stop	stop/1	0.96	0.97	-	8.3	8.3
		15	stop	stop/1	0.95	0.96	-	9.9	9.9
		30	stop	stop/1	0.93	0.94	-	13.5	13.5
		45	stop	stop/1	0.89	0.90	-	17.3	17.3
		60	stop	stop/1	0.38	0.43	-	20.8	20.8
15	0.2	0	stop	stop/1	0.89	0.89	-	2.3	2.3
		15	stop	stop/1	0.87	0.87	-	4.5	4.5
		30	stop	stop/1	0.82	0.82	-	7.3	7.3
		45	stop	stop/1	0.73	0.73	-	10.4	10.4
		60	stop	stop/1	0.02	0.03	-	13.4	13.4
	0.33	0	stop	stop/1	0.89	0.89	-	2.3	2.3
		15	stop	stop/1	0.86	0.86	-	5.7	5.7
		30	stop	stop/1	0.80	0.80	-	10.3	10.3
		45	stop	stop/1	0.69	0.70	-	15.2	15.2
		60	stop	stop/1	0.02	0.03	-	20.1	20.1

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 7% of the time. Whereas the probability of selecting a good dose is between 60 and 82%. As the size of the AR phase increases from 0 to 60 so do the selection probabilities for a good dose, going from 60% to 80% and 60% to 82% for randomisation probabilities of 0.2 and 0.33 respectively. It should be noted that the two designs with no AR phase are identical since the randomisation probabilities are never used. Overall, the different parameterisations perform similarly however, an argument could be made that those with a higher probability of randomising to control are better optimised since they achieved similar selection probabilities whilst allocating more patients to the control dose. In terms of the number 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 fewer patients are being treated at good doses at higher AR sizes. Also, the  $\phi_R$  figure does not guarantee that exact percentage of patients in the control dose will be allocated to control but for this scenario it appears to be somewhat accurate.

Scenario 2 has no OBD as all treatment doses are considered toxic. For most of the combinations, stopping occurs 67-81% of the time and including allocation to the control arm we see this increase to 70-85%. Slightly concerning is the case where the AR phase lasts the whole trial. Here stopping is less frequent at 50% and 42% 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 consonantly be allocating patients to control. As such it may be the case that not enough toxicity events are being collected to recommend stopping. 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 toxic at high doses and ineffective at the lower doses meaning only one dose can be considered good or the OBD. This is a difficult scenario since only one of the five dose-levels is suitable to allocate patients to. The selection probabilities range from 25% to 52%. We see as  $j_R$  increases selection probabilities also increase. As those designs with smaller AR phases go into the maximisation phase they would be selecting dose-levels based on those in the admissible set with higher efficacy. Since the doses with higher efficacy also have a high toxicity rate there is a chance early on in the trial this isn't detected resulting in toxicities at the higher dose-levels causing the trial to stop early. This could be a reason as to why the designs with the larger AR phase perform better as doses would be randomly selected. Meaning more chance for the lower dose-levels to be chosen and since those aren't toxic and the futility rule doesn't kick in until the maximisation phase there's a higher chance that the OBD can be found.

Scenarios 4-6 look at a unimodal dose-efficacy relationship where efficacy peaks at dose-level 3, with the three same dose-toxicity relationships as before: tolerable, toxic and toxic at high doses for each scenario respectively. Firstly, scenario 4 we see good performance from all the paramterisations with the probability of selecting the OBD ranging between 68% and 73% and the probability of selecting a good dose ranging from 75% to 84%. We also see an



appropriate amount of patients in the control arm for each of our parameter combinations. An important characteristic of this design to note is the ratio of patients allocated to the control arm compared to the OBD or the good doses. For the higher randomisation probability and maximum AR phase we can see close to a 1:1 (18.5 at good dose levels to 19.5 at control) allocation between patients treated at control and at the best doses. For  $\phi_R = 0.2$ , and  $j_R = 45$  we can see close to a 2:1 allocation between those treated at the OBD (21.6) and those treated at the control (9.5).

Scenario 5 is where treatment is too toxic, like scenario 2 we see high probabilities of stopping 67%-81% and stopping plus including patients in the control arm 70%-86%. Similarly, the design with an AR phase of 60 performs poorly here and the number of the patients allocated to the control is also comparable.

Scenario 6 only has one good dose to select, making it similar to scenario 3 except with a unimodal efficacy curve. Here, selection probabilities are slightly better ranging from 37%-59%. In this scenario we also observe that the larger the AR phase the greater the selection probability of the OBD. The unimodal efficacy curve means that the dose we want to select is also the dose with the highest efficacy making it easier for the model to pick out.

A plateau relationship where dose-efficacy stops increasing after dose 3 is looked at in scenarios 7-9 with the three different toxicity curves. In scenario 7 the probability of selecting the OBD ranges from 48%-56%, with the probability of selecting a good dose ranging from 70-84%. In this instance we see quite a bit of discrepancy going from selecting the OBD to selecting the good doses in terms of the selection probabilities being much higher for good doses. Here we have three doses with the same efficacy level, two of which only have a slight increase in toxicity, which is still below the pre-specified target level. This can also be seen in the number of patient being treated at the good dose versus at

the OBD. Scenario 8 exhibits the same behaviour as the other toxic scenarios 2 and 5. Then with scenario 9, the designs also behave similarly to scenarios 3 and 6 where higher dose-levels are too toxic. Selection probabilities range from 34% to 56% with the designs with higher AR phases performing better.

For scenarios 10-12 we look at a monotone decreasing efficacy curve where dose-level 2 is the most efficacious for each of the toxicity curves. In scenario 10 we see very high probabilities of selecting the OBD 76%-80% with the probability of selecting a good dose being 97% or higher. We can also see that in terms of the numbers treated at the OBD and the good doses as these values are relatively high compared to other scenarios. As the OBD is one of the lower dose-levels it makes it relatively easy for the model to select since it's more likely that patients will be allocated there early on into recruitment. Once the maximisation phase starts there would be a lot of efficacy data for that dose and it would be favoured by the model. Even in the cases with larger AR phases the adaptive randomisation probabilities are still scaled based on efficacy, so it would be more likely they would be allocated to dose-level 2 as well.

In terms of stopping early if the dose-levels are too toxic for this efficacy curve, scenario 11, it seems to perform worse compared to other scenarios where all the dose-levels are too toxic. Even so, we still see the same patterns where when the AR phase is 60, the same size as the trial stopping is relatively even worse. Ignoring those designs the stopping probability ranges from 52%-65%, adding in the percentage of patients allocated to the control arm this increases to 56%-74%. One reason why this may be worse is due to the very high efficacy rates early on and the toxicity rate only being slightly above our target rate by 5%. Early on into the trial that 5% would be difficult for the model to detect but the high efficacy rate is likely to lead to more events so the trial would be less likely to stop until it went to higher dose-levels.

Typically, the scenarios where the higher doses are more toxic have been the most difficult for the design to deal with. However for scenario 12, with the monotone decreasing efficacy curve we see probabilities of selecting the OBD be range from 80%-85%. This is even higher than selection probabilities in scenario 10. One possible reason for this may be that when escalating, more toxicities are observed reducing the admissible set of doses to the earlier dose-levels which contains the OBD. When we look at the probabilities of selecting good doses (92%-97%), whilst still very high its still slightly less than in scenario 10 where there was one more dose which could be considered good.

Finally the last efficacy curve we look at is one where no efficacy is apparent, so efficacy stays at the same level as the control dose. Ideally in all these scenarios (13-15) we would stop for lack of efficacy. One thing to point out is that the rule for stopping for futility only triggers in the maximisation phase. So, for the designs where  $j_R = 60$  stopping for lack of efficacy will not occur. For scenario 13 we have doses which are all tolerable and can see stopping probabilities ranging from 54% to 82%. The only reason to stop in this scenario is for lack of efficacy and so those designs with larger AR phases won't be able to do this till later on into the trial meaning they are less likely to stop as reflected in the stopping probabilities. In terms of selecting the good dose, this is identical to selecting the OBD. So, in this scenario the control dose is almost never selected as the OBD, even though patients are still being allocated to that dose-level. As stated for AR phase size of 60 the trial cant be stopped for futility, so the probability it stopping is due to toxicity. In scenario 14, all the dose-levels are toxic, here we have very high stopping rates between 89%-96% except in the case of when the AR phase is 60. Scenario 15, where only the higher doses are too toxic stops most of the time as well given a reasonable AR phase between 69% and 89% of the time. Again, very rarely is the control dose selected as the OBD.

Table 3.4 provides a summary and summary statistics of the selection probabilities of the OBD and good doses respectively for all 15 scenarios and 10 parameter combinations. The mean provides a rudimentary glance across the 15 scenarios of how well it selects the OBD / good dose-levels. The standard deviation is a representation in the variability of performance across the different designs. The lower the standard deviation the more homogenous the performance. These statistics have been calculated for all scenarios and then for 'Non Stopping' scenarios, which is just the scenarios where stopping early for toxicity/futility isn't the ideal outcome i.e. scenarios 1,3,4,6,7,9,10 and 12.

The means for selecting a good dose are about 10% higher and appear to be slightly less variable, this is to be expected as when selecting the good dose-levels we are allowing for a wider range of doses to be included. There appears to be limited differences between the various parameterisations, except for in the case of when  $j_R = 60$  where its performance is poor in scenarios which require stopping. There are only 1-2 percentage points difference in the mean selection of the OBD and good dose-levels for the various designs.

TABLE 3.4: Probabilities of selecting the OBD and good dose levels for multiple combinations of AR phase size and probabilities for randomisation to control, plus summary statistics.

$\phi_R$	$j_R$	Probability of selecting good dose levels: Scenarios 1-15															All scenarios		Non Stopping	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	StDev	Mean	StDev
Selection probabilities for the OBD																				
0.20	0	0.05	0.81	0.25	0.69	0.81	0.37	0.48	0.81	0.34	0.77	0.65	0.83	0.82	0.96	0.89	0.63	0.27	0.47	0.27
	15	0.05	0.80	0.31	0.69	0.79	0.41	0.50	0.79	0.36	0.79	0.65	0.83	0.78	0.95	0.87	0.64	0.25	0.49	0.26
	30	0.05	0.77	0.35	0.71	0.77	0.45	0.52	0.77	0.42	0.79	0.62	0.82	0.70	0.94	0.82	0.63	0.23	0.51	0.26
	45	0.05	0.72	0.42	0.73	0.71	0.50	0.56	0.71	0.45	0.79	0.57	0.84	0.57	0.92	0.73	0.62	0.21	0.54	0.26
	60	0.04	0.41	0.48	0.71	0.41	0.54	0.57	0.41	0.50	0.80	0.41	0.85	0.01	0.42	0.02	0.44	0.26	0.56	0.25
0.33	0	0.05	0.81	0.25	0.69	0.81	0.37	0.48	0.81	0.34	0.77	0.65	0.83	0.82	0.96	0.89	0.63	0.27	0.47	0.27
	15	0.07	0.77	0.32	0.69	0.78	0.42	0.49	0.78	0.38	0.77	0.64	0.81	0.76	0.95	0.86	0.63	0.24	0.49	0.25
	30	0.06	0.75	0.39	0.70	0.75	0.50	0.51	0.75	0.45	0.76	0.60	0.80	0.68	0.93	0.80	0.63	0.22	0.52	0.24
	45	0.05	0.67	0.46	0.70	0.67	0.55	0.55	0.69	0.52	0.76	0.52	0.81	0.54	0.89	0.69	0.60	0.20	0.55	0.24
	60	0.03	0.38	0.52	0.68	0.38	0.59	0.56	0.38	0.56	0.78	0.38	0.82	0.01	0.38	0.02	0.43	0.26	0.57	0.24
Selection probabilities for good dose-levels																				
0.20	0	0.60	0.85	0.25	0.75	0.86	0.37	0.70	0.85	0.34	0.97	0.74	0.92	0.82	0.97	0.89	0.73	0.23	0.61	0.27
	15	0.65	0.85	0.31	0.76	0.84	0.41	0.73	0.84	0.36	0.97	0.72	0.93	0.78	0.96	0.87	0.73	0.21	0.64	0.26
	30	0.71	0.81	0.35	0.81	0.82	0.45	0.78	0.81	0.42	0.98	0.69	0.95	0.70	0.95	0.82	0.74	0.19	0.68	0.25
	45	0.76	0.75	0.42	0.83	0.75	0.50	0.81	0.76	0.45	0.99	0.63	0.96	0.57	0.93	0.73	0.72	0.18	0.71	0.23
	60	0.80	0.50	0.48	0.83	0.49	0.54	0.82	0.50	0.50	0.99	0.49	0.97	0.01	0.50	0.03	0.56	0.29	0.74	0.21
0.33	0	0.60	0.85	0.25	0.75	0.86	0.37	0.70	0.85	0.34	0.97	0.74	0.92	0.82	0.97	0.89	0.73	0.23	0.61	0.27
	15	0.67	0.83	0.32	0.77	0.83	0.42	0.75	0.82	0.38	0.97	0.72	0.94	0.76	0.96	0.86	0.73	0.21	0.65	0.25
	30	0.75	0.79	0.39	0.81	0.78	0.50	0.80	0.79	0.45	0.98	0.67	0.95	0.68	0.94	0.80	0.74	0.18	0.70	0.23
	45	0.79	0.70	0.46	0.84	0.70	0.55	0.84	0.71	0.52	0.99	0.56	0.96	0.54	0.90	0.70	0.72	0.17	0.74	0.21
	60	0.82	0.42	0.52	0.83	0.43	0.59	0.84	0.43	0.56	0.99	0.42	0.97	0.01	0.43	0.03	0.55	0.30	0.76	0.18

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. For the randomisation probabilities, performance was mostly similar between the two values we chose. Many of the discrepancies in the scenarios were due to the size of the AR phase. Seemingly, performance was generally unaffected by the percentage of patients being randomised to control but rather the amount of time spent being randomised. In terms of patient numbers at the control dose we see on average a similar number 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 values ranging from 9.4 to 15.6 across the 15 scenarios.

Based on these simulations it would be best to use an AR phase sized between 25% and 75% of the total sample size and a randomisation to control probability that will produce the desired number of control patients. This can be determined by dividing the desired number of controls by the size of the AR phase. For example, say our AR size is 30 patients and we want 15 controls the probability of randomising to control  $\phi_R$  should be set to 0.5 (15/30). 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 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 to 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 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 an ODB. 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 straightforward 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 upfront a guaranteed number of patients can be expected in the control arm, which may be a desirable characteristic of this design. It is important to note in our simulations here that we will not consider any data from the patients in the control arm to have an impact on the dose-finding study arm. Both arms can be considered independent for the purposes of our simulations. 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  $j_R = 30$  and  $\phi_R = 0.33$  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 30 and a probability of randomising to control at 33%. Here we would expect roughly ten patients to be allocated to the control arm (33% of 30), looking at Table 3.3 for this combination we see on average we achieve around 9-10 patients at the control dose-level in non-toxic scenarios. 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. Alternatively, if the number of control patients desired is known the denominator can be replaced by that number. In this scenario, this corresponds to a 1:5.06 randomisation which would lead to 10 patients in the control arm and 50 in the dose-finding study. As we are using cohorts of 3 it would be preferable to have the sample size of the dose-finding study be divisible by 3. Therefore we set the desired number of control patients as 9, leaving 51 for the dose-finding study. This gives a randomisation ratio of 1:5.67 (3:17).

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. We summarise the three designs being compared in Table 3.5.

To compare these different approaches simulations will be used covering the same 15 scenarios as in section 3.4.2. For each scenario, we simulate 10000 trials each using the designs mentioned above. Table 3.6 shows the operating characteristics comparing the three designs. Table 3.7 provides summary statistics of the operating characteristics.



TABLE 3.5: Summary of the three designs being compared.

Design	Specification	Benefits	Flaws	Assumptions
RtC-WT	5 Doses N = 60 Cohort size = 3 AR size ( $j_R$ ) = 30 $\phi_R = 0.33$	Guaranteed patients recruited to the control dose. Able to compare control to experimental doses.	Performance may suffer. Extra complexity in the design.	The lowest dose level is a control dose.
WT	5 Doses N = 60 Cohort size = 3 AR size ( $j_R$ ) = 30	Better performance. Simple to implement. Able to compare control to experimental doses.	Patients not guaranteed at the control dose.	Control dose treated in the same way as an experimental dose.
Two-Arm	4 Doses N = 51 Cohort size = 3 AR size ( $j_R$ ) = 24	Simpler to implement. Exact number of control patients is known.	Cannot include the control dose when modelling toxicity and efficacy	Recruit dose-finding and control patients separately. Allocation ratio is based on the number of control patients desired.

TABLE 3.6: Operating characteristics for alternative designs. Probability of selecting the best or good dose levels as the OBD, mean number of patients treated at those dose levels and at the control dose after 10000 simulations.

Scenario	Design	OBD	Good Doses	P(OBD)	P(Good)	N(OBD)	N(Good)	N(Control)
1	RtC-WT	5	3-5	0.06	0.75	2.2	30.4	9.8
	WT	5	3-5	0.05	0.72	2.1	31.8	6.6
	Two-Arm	5	3-5	0.04	0.61	1.8	25.5	9
2	RtC-WT	stop	stop/1	0.75	0.79	-	14	14
	WT	stop	stop/1	0.76	0.80	-	13.9	13.9
	Two-Arm	stop	stop	0.75	0.75	-	-	9
3	RtC-WT	3	3	0.39	0.39	17.3	17.3	10.4
	WT	3	3	0.37	0.37	17.7	17.7	8.4
	Two-Arm	3	3	0.26	0.26	12.6	12.6	9
4	RtC-WT	3	3-4	0.70	0.81	24.8	31	9.9
	WT	3	3-4	0.73	0.81	27.6	33.5	6.6
	Two-Arm	3	3-4	0.72	0.76	24	28.1	9
5	RtC-WT	stop	stop/1	0.75	0.78	-	14.1	14.1
	WT	stop	stop/1	0.76	0.80	-	13.9	13.9
	Two-Arm	stop	stop	0.75	0.75	-	-	9
6	RtC-WT	3	3	0.50	0.50	20.3	20.3	10.4
	WT	3	3	0.48	0.48	21.2	21.2	8.4
	Two-Arm	3	3	0.38	0.38	15.9	15.9	9
7	RtC-WT	3	3-5	0.51	0.80	20.8	31.6	9.7
	WT	3	3-5	0.54	0.79	22.8	33.4	6.8
	Two-Arm	3	3-5	0.52	0.71	19.5	27.8	9

TABLE 3.6: Operating characteristics (continued)

Scenario	Design	OBD	Good Doses	P(OBD)	P(Good)	N(OBD)	N(Good)	N(Control)
8	RtC-WT	stop	stop/1	0.75	0.79	-	14	14
	WT	stop	stop/1	0.75	0.79	-	13.9	13.9
	Two-Arm	stop	stop	0.76	0.76	-	-	9
9	RtC-WT	3	3	0.45	0.45	18.6	18.6	10.4
	WT	3	3	0.43	0.43	19.4	19.4	8.4
	Two-Arm	3	3	0.34	0.34	14.2	14.2	9
10	RtC-WT	2	2-4	0.76	0.98	34.6	49.1	9.8
	WT	2	2-4	0.78	0.98	36.4	52.2	6.7
	Two-Arm	2	2-4	0.83	0.99	37.1	50.2	9
11	RtC-WT	stop	stop/1	0.60	0.67	-	14.7	14.7
	WT	stop	stop/1	0.60	0.67	-	14.3	14.3
	Two-Arm	stop	stop	0.53	0.53	-	-	9
12	RtC-WT	2	2-3	0.80	0.95	36.6	46.3	10.4
	WT	2	2-3	0.82	0.95	38.5	48.5	8.3
	Two-Arm	2	2-3	0.90	0.97	41.2	48.6	9
13	RtC-WT	stop	stop/1	0.68	0.68	-	9.7	9.7
	WT	stop	stop/1	0.71	0.71	-	6.3	6.3
	Two-Arm	stop	stop	0.68	0.68	-	-	9
14	RtC-WT	stop	stop/1	0.93	0.94	-	13.5	13.5
	WT	stop	stop/1	0.94	0.95	-	13.2	13.2
	Two-Arm	stop	stop	0.95	0.95	-	-	9
15	RtC-WT	stop	stop/1	0.80	0.80	-	10.3	10.3
	WT	stop	stop/1	0.82	0.82	-	8.1	8.1
	Two-Arm	stop	stop	0.81	0.81	-	-	9

In order to compare the Two-Arm design with the others we still consider there to be five dose-levels, with the first dose-level being a separate arm and dose-levels 2-5 comprising the dose-finding arm. Also, since the two arms can be considered independent in scenarios where stopping is preferred, this

TABLE 3.7: Probabilities of selecting the OBD and good dose levels for multiple designs, plus summary statistics.

Design	Selection probabilities: Scenarios 1-15															All scenarios		Non Stopping	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean	StDev	Mean	StDev
<b>Selection probabilities for the OBD</b>																			
RtC-WT	0.06	0.75	0.39	0.70	0.75	0.50	0.51	0.75	0.45	0.76	0.60	0.80	0.68	0.93	0.80	0.63	0.22	0.52	0.24
WT	0.05	0.76	0.37	0.73	0.76	0.48	0.54	0.75	0.43	0.78	0.60	0.82	0.71	0.94	0.82	0.64	0.23	0.53	0.26
Two-Arm	0.04	0.75	0.26	0.72	0.75	0.38	0.52	0.76	0.34	0.83	0.53	0.90	0.68	0.95	0.81	0.62	0.26	0.50	0.30
<b>Selection probabilities for good dose-levels</b>																			
RtC-WT	0.75	0.79	0.39	0.81	0.78	0.50	0.80	0.79	0.45	0.98	0.67	0.95	0.68	0.94	0.80	0.74	0.18	0.70	0.23
WT	0.72	0.80	0.37	0.81	0.80	0.48	0.79	0.79	0.43	0.98	0.67	0.95	0.71	0.95	0.82	0.74	0.19	0.69	0.24
Two-Arm	0.61	0.75	0.26	0.76	0.75	0.38	0.71	0.76	0.34	0.99	0.53	0.97	0.68	0.95	0.81	0.68	0.22	0.63	0.28

would only stop the dose-finding arm so patients at dose-level 1, the control arm, can still be recruited.

Performance of the RtC-WT and WT design are quite similar across all the scenarios. There only appears to be a difference between 1 and 2% in selection probabilities. At a given time-point, for the RtC-WT design we expect the adaptive randomisation probabilities for the experimental doses to be lower than those in the standard WT design as we are assigning a fixed probability to be randomising to the control arm. This means it would be less probable for the RtC-WT to allocate to a relatively higher efficacious dose in the admissible set. As such, we'd expect the WT design to constantly outperform the RtC-WT design. It's noteworthy that under the monotone increasing (scenarios 1 and 3) and plateau efficacy relationships (scenarios 6 and 9) the RtC-WT actually has slightly higher selection probabilities. One reason for this may be due to the underlying example trial we are using where the efficacy rate in the control dose is relatively high, at 30%, to begin with. Meaning the standard WT design would have a small adaptive randomisation probability for assigning patients to that control dose without forcing anything.

Consistently the RtC-WT and WT designs outperform the Two-Arm approach in terms of selection of the OBD if only by a few percentage points. Since the Two-Arm approach is essentially the same as the standard WT design but with fewer patients, it is expected to be slightly inferior as with most

dose-finding studies a higher number of patients yield better operating characteristics. However, with the RtC-WT design actively recruiting to the control dose there should be an equal number of patients receiving control and treatment dose-levels to equate to similar operating characteristics. There appears to be some added benefit in terms of modelling for including control as a dose-level rather than using the Two-Arm approach when it comes to selecting the OBD. It should be mentioned that the differences in selection of the OBD are only slight between 1% and 8%. Also, the Two-Arm approach manages to allocate more patients to the OBD in certain scenarios (10 and 12) which is the monotone decreasing efficacy curve. In these scenarios having fewer dose-levels is an advantage as the earlier dose-levels are the most optimal making selection easier. It should be mentioned that an alternative specification of the Two-Arm approach may lead to better performance overall. In scenarios where stopping early would be ideal all three designs seem to behave similarly and have relatively comparable operating characteristics.

The key differences between RtC-WT and WT can be seen in the number of patients recruited to the control dose-level. The WT design recruits fewer patients here as expected since the randomisation probability isn't fixed. This usually results in more patients being allocated to the OBD. RtC-WT would experience situations where it would allocate a cohort to the control dose-level but the standard WT in the same situation would be able to randomise between the efficacious doses. This advantage however does not consistently yield better selection probabilities. Generally we can say the WT design is not ideal if a trial aims to recruit control patients whilst conducting a dose-finding study. However, in the case where the control dose has high enough efficacy the WT design can successfully still randomise patients there as can be seen in these simulations. It's possible under a different parametrisation, perhaps a design with a larger adaptive randomisation phase those numbers of control patients

would be higher, although this may negatively impact performance. Overall, we can see the trade-off between allowing for this recruitment to control and overall performance. Based on these simulations and scenarios it seems RtC-WT performs relatively well.

## 3.5 Discussion

In this chapter we proposed RtC-WT, an extension to the seamless Phase I/II Wages & Tait trial design to allow for the ability to randomise patients to a control dose. The main motivation was to add a control arm as a dose level to achieve similar objectives as a randomised phase II study whilst maintaining efficiency in the dose-finding process. We examined the impact of various combinations of the AR phase size and the probability of randomising to control. We then compared RtC-WT to alternative approaches. We also assessed the impact of different efficacy skeletons and assumptions we made about the control dose on the designs operating characteristics. In summary, we found that RtC-WT maintains reasonable operating characteristics when randomising patients to a control dose, although this depends on the parametrisation of the design.

When examining the various combinations of AR phase sizes and randomisation to control probabilities we consistently saw several issues with the extreme values of AR phase sizes. For instance, when the AR phase lasts the whole trial the design had some issues stopping for excess toxicity. There were also problems generally for the design when attempting to stop for futility. It may be necessary to employ alternative stopping rules to achieve acceptable probabilities of stopping in certain scenarios. Also, when there was no AR phase the design had issues locating the OBD. This lead to the recommendation of using 25-75% of the trial size as the AR phase as these were the values

we investigated.

In terms of randomisation probabilities, we looked at two different possibilities in conjunction with the various AR phase sizes. There are practically countless combinations that could have been investigated and different combinations may have led to alternative conclusions. What can be said however is that in a practical clinical trial setting thought should be given to how many patients investigators want to recruit to control then using that to determine the optimal sample size and AR phase size. For example, if 20 control patients are desired from a maximum sample size of 60 a randomisation to control probability of 0.66 for an AR phase size of 30 could be used or a 0.5 randomisation provability with an AR size of 40. Also, here it may be unfeasible to look at every combination but a sample should be investigated to see how it impacts the design.

Furthermore, the scenarios we presented in our simulations are again only a small handful of all possible scenarios that could be investigated. The scenarios we chose represent a variety of dose-efficacy curves which may be plausible in this trial setting. Another limitation of the simulations is how toxicity and efficacy data were generated. We have assumed that both of these events are independent but in a practical scenario this may not be the case. A patient may withdraw from the trial after having a toxicity meaning no efficacy data can be observed for that individual. Further work could be done to look at the impact of sampling dependent toxicity and efficacy data.

To our knowledge, there are no other phase I/II designs that share the same aims as RtC-WT as such it is difficult to make comparisons with alternative approaches. We opted to compare our design against an easy to implement two-arm method. Although our design outperformed the two-arm approach in the scenarios presented we did not optimise the design of the dose-finding

arm. Usually specifying a design for a dose-finding study is an iterative process in which certain parameters are tweaked to produce optimal operating characteristics. As such a more optimised two-arm approach could yield better performance than RtC-WT. The same could be said for the RtC-WT design and there could exist a better combination of parameters for the example trial we presented.

For all our simulations and when comparing designs we used the same exemplar trial. This involved a control dose which had a known toxicity and efficacy profile. The probability of observing an efficacious event at this dose was specified at 30%. Even though this is relatively high when comparing our design directly to a standard Wages and Tait design we saw an increase in the number of patients at the control dose and no real loss in terms of performance. This shows our design achieves what was intended as well as the fact that the standard Wages and Tait design can perform a similar job if the efficacy rates of the control dose is high enough. One caveat to this however is that we have just looked at one example trial and these conclusions may vary for a trial in which the control dose isn't quite as efficacious. Further work could be done comparing these designs using different trials with different underlying assumptions.

If choosing between these two designs to be implemented into an actual trial there may be multiple things to consider. Whilst the RtC-WT and WT perform similarly in these simulations in practice this may not be the case. The RtC-WT may be a more flexible option. For example in the case where it is assumed that the control dose would have a relatively high probability of efficacy, simulations would show a number of patients being recruited to that dose however, if in the actual trial the efficacy rate at the control dose is much lower than anticipated you would end up with fewer patients at that dose than the initial simulations would suggest. With the RtC-Wt this would

not be the case since the probability to randomise to the control dose is fixed up front and would remain constant throughout a variety of scenarios as we have demonstrated.

There may also be many practical considerations to accommodate when considering implementing RtC-WT into an actual trial. For example, the adaptive randomisation component may require validation from multiple statisticians every time the probabilities are updated. In the case of RtC-WT this would need to be done for each cohort. As statisticians are a rare resource in most trials units this may be a limitation to using the design. It could be said however in the case of Wages and Tait and other dose-finding trials which use adaptive randomisation that patients aren't being adaptively randomised but rather the dose-levels are. This distinction may circumvent the need to have the randomisation probabilities validated. Typically, in normal dose-finding studies patients who enter the trial later on are more likely to receive the higher dose-levels dependent on whatever escalation occurred so far. With RtC-WT and Wages and Tait method in general patients will be able to receive any of the admissible doses with probabilities scaled to the most efficacious doses.

It should be noted that the inclusion of a control dose depends on the definition of efficacy and toxicity events. It should be possible to measure the efficacy and toxicity events in the control arm. For example, standard of care may aim to treat the underlying symptoms of a condition whereas the treatment aims to reduce some biological measure that standard of care doesn't impact. This is more of a practical concern to determine if RtC-WT is a suitable design for a trial since during the modelling phase if no toxic or efficacy events are observed for the control this shouldn't be an issue.

A recent development by Yan et al. [42] suggested three alternative strategies of adaptive randomisation for the Wages and Tait design. They showed



that their final recommended strategy achieved better accuracy when selecting the OBD as well as allocating more patients to that dose-level as well. The strategy works by gradually excluding efficacy skeletons as data is collected. RtC-WT could be improved further by the incorporation of this alternative adaptive randomisation method as we have already shown its effectiveness in comparison to the traditional Wages and Tait design.

Whilst relatively simplistic our modification allowed for the inclusion of a control dose-level to the Wages and Tait method without compromising operating characteristics. We presented results from multiple simulations showing good performance, especially in non-monotonic efficacy scenarios. Further work could be done to consider a wider range of design specifications and scenarios. We utilised a relatively simple trial scenario and made a lot of assumptions that may not necessarily be applicable in a real-world trial setting.



## Chapter 4

# Extending Dose Transition

# Pathways for use in TITE-CRMs

### 4.1 Introduction

The continual reassessment method (CRM) was first introduced by O’Quigley et al. [10] in 1990. This methodology was developed as an approach to meet ethical requirements and use models to reasonably approximate the true probability of toxicity around the dose close to the target toxicity. At the time sequential designs such as the 3+3 were commonly used in Phase I oncology trials and met many of the requirements to do so. However, even at the time, there were many criticisms of these approaches as patients may be treated sub optimally, poor operating characteristics and that the recommended dose or MTD has limited interpretation as a dose yielding a specific target toxicity. In their paper O’Quigley et al. [10] demonstrate the CRM’s superiority over various sequential designs via simulations. The main advantage of the CRM is that it is able to make use of all accumulated data whereas designs such as the 3+3 make decisions and recommendations based on data from the most recent cohort of patients.

With the CRM debuting over 30 years ago in the literature and multiple

papers over the years confirming its advantages over rule-based designs you would expect model based approaches for dose-finding trials to become the norm however, this is not the case. A study by Rogatko et al. [11] published in 2007 looked into the translation of effective statistical designs into phase 1 trials for new anticancer therapies. Between 1991 and 2006 they searched for abstracts and categorised them as either clinical dose-finding trials or statistical methodology for dose-escalation trials. They found 1235 clinical trials and 90 methodological papers. Of those 1235 trials only 20 (1.6%) used statistical methodology, the remaining papers used various rule-based designs. Another paper by Chiuzan et al. [12] looked at the number of phase I oncology articles published between 2008 and 2014. Out of the 1712 dose-finding trials 1591 (92.9%) used rule-based designs.

Based on these reviews we can see that the uptake of more efficient Bayesian designs such as the CRM has been slow and limited. There are probably a number of factors which cause this such as lack of resources, access and understanding. The main issue is that implementation of these designs usually require the input of a statistician more specifically one who is familiar with these designs. They also need to be able to implement and conduct the trial with software available, for designs such as the CRM there are multiple options available such as the R packages `dfcrm` [27] and `escalation` [41]. However, for more complex and innovative designs software may not be readily accessible and implementation may be difficult, for example the implementation of the PO-TITE-CRM design which was the topic of Chapter 2. As early phase trials work with less resources i.e less patients, time, money etc. it would be advantageous to use designs which are more efficient with the data collected, the majority of which would require a statistician to implement. Funding for a statistician may not be available so clinicians would have to opt for these rule-based designs which are much easier to implement as dose escalation

follows a set procedure based on the outcomes observed and doesn't require any statistical input. Clinicians may also not be familiar with these complex designs and how they work.

Dose transition pathways (DTP), were developed as tool by Yap et al. [43] in order to address some of the issues around understanding and implementation of these complex and innovative designs. DTPs can be considered a tool primarily for dose-finding trials where the primary objective is to determine a MTD (or TD<sub>50</sub> at a specific target toxicity level) which is determined by the occurrence of DLTs recorded as a binary variable. The purpose of DTPs is to aid the design and analysis of these types of trials. This is done by projecting in advance the dose-escalation decisions for future cohorts based on data accrued. It can also be used as a calibration tool during the design phases of a trial to ascertain how the model behaves under certain outcomes and modify its specifications if necessary. These projections can then be visualised and help illustrate how the model operates and communicate possible future decisions that may be made.

In the paper by Yap et al. [43] originally introducing DTPs they use the example of a trial with a CRM design. They discuss that the idea of DTPs can be extended to other model based designs such as the TITE-CRM and phase I/II designs that consider efficacy and toxicity. DTPs are produced based on the outcome data collected and for both of these possible extensions the outcome data is slightly more complex which makes producing DTPs for these designs challenging. Specifically, for the TITE-CRM additional data is needed dependent on if the patient is to be fully or partially weighted. That is if the patient has not experienced a DLT they will be partially weighted in the model based on the time they have spent in the trial. This makes mapping out dose-escalation decisions difficult since we are no longer dealing with a simple binary variable of DLT/no DLT.

In this chapter we aim to explore the potential of extending DTPs for use in TITE-CRMs. We start by providing an example of a DTP for a simple CRM design to better understand what they are and how they can be used. We then look at some of the issues with extending DTPs to TITE-CRMs and present possible solutions for how they may be overcome.

## 4.2 Dose Transition Pathways

In order to explore how DTPs can be extended for use in TITE-CRMs we first look how they would be implemented/used for a simple CRM trial. To do this we look at how CRM designs are implemented and analysed and how DTPs can be incorporated in these processes.

When implementing a CRM design multiple parameters need to be considered and specified. These are: number of doses, target toxicity level, dose-toxicity model, dose-toxicity skeleton, method of inference, decision rules, sample size, cohort size, safety modifications, and stopping rules [44]. This usually requires the input from multiple sources such as the statistician, clinician and trial management team. Typically, once these parameters have been specified simulations can be run for various clinically relevant scenarios to obtain operating characteristics for the specified CRM design. At this point these results can be reassessed and the specifications of the CRM can be updated and this whole process can be repeated until an acceptable design is reached.

Even after multiple rounds of simulations there is still the risk that a statistically optimal design may not be optimal in practice. This could be due to the scenarios used in simulations not being representative of what is observed during the running of the trial. This may also occur when model recommendations are deemed clinically inexplicable and dose-escalation decisions recommended by the model are deviated from. Whilst dose recommendations

from the model should be used as guidance if its recommendations are constantly being ignored it undermines the model and brings into question its specifications. DTPs can be used to avoid this from occurring and can help calibrate the model, by providing insight during the design phase of the trial into what recommendations the model is making. This will help clinicians as well as statisticians better understand how the model works and calibrate it accordingly so clinically reasonable decisions are being made.

DTPs can also be utilised during the analysis of a trial. In a 3+3 trial just by knowing the rules of the design we already know what dose-escalation decision will be made for all possible outcomes of one cohort. If zero out of three patients (0/3) experience a DLT we escalate to the next highest dose; if one out of three patients (1/3) experiences a DLT we recruit a further 3 patients to the same dose-level; and if two out of three (2/3) patients experience a DLT we de-escalate to a lower dose or stop the trial if already at the lowest dose. This can be done and computed without the need of a statistician. On the other hand, we have designs such as the CRM where this is not as simple since the next recommended dose will be based on the accrued data. Here DTPs can be utilised and present this information by analysing all possible outcomes and presenting the dose recommendations these lead to.

The number of pathways can be calculated using the number of cohorts ( $x$ ) and the number of patients in each cohort ( $y$ ). Here, the total sample size is  $xy$  and the number of pathways is  $(y + 1)^x$ . So, for a trial recruiting 10 cohorts of 3 patients the number of pathways would be over 1 million ( $[3 + 1]^{10} = 1,048,576$ ). Its possible that there may be less pathways based on any stopping rules which cause the trial to stop early. Obviously, presenting this many pathways is difficult and may also be unintuitive. Yap et al. [43] suggest using the first group of cohorts to help facilitate discussion with investigators

during the design phase of the trial. DTPs can also be updated during dose-escalation phases as well by incorporating the accrued data then projecting pathways for subsequent cohorts. In the next section, section 4.2.1 we provide a generic trial example to show how DTPs can be implemented.

### 4.2.1 Example trial to illustrate DTPs

Lets consider an early phase trial aiming to determine the TD25 of a single agent, Table 4.1 details all the parameters we need to set-up the CRM design. First we specify the clinical parameters; there will be 5 dose levels ( $d_1, \dots, d_5$ ), the trial will start at dose-level 2 ( $d_2$ ), the target sample size will be 30 patients, patients will be recruited in cohorts of 3 (10 cohorts overall) and the target DLT rate will be 25% (TD25). A single-stage CRM will be used with a power model to model the dose-toxicity curve, Bayesian estimation methods will also be used. We assume the prior distribution for the slope parameter in the power model will be normally distributed with a mean of 0 and variance of 1.34. Initial guesses for the DLT rates are specified as 0.04, 0.08, 0.16, 0.25 and 0.35 for dose-levels 1-5 respectively, this assumes dose-level 4 ( $d_4$ ) will be the TD25.

TABLE 4.1: Specification of parameters for an example CRM trial.

Parameter	Value
Number of dose-levels	5
Starting dose-level	2
Sample size	30
Cohort size	3
Target DLT rate	25%
Dose-toxicity model	Power model
Dose-toxicity skeleton	0.04, 0.08, 0.16, 0.25, 0.35
Method of inference	Bayesian

Most of the parameter specifications made here are fairly arbitrary, in practice these specifications should have either a clinical or statistical rationale behind them based on the context of the trial which requires input from multiple



parties. Once an initial set of the se parameters have been selected, it's usually at this stage that simulations take place in order to assess the operating characteristics of the design under various scenarios. At this point DTPs can also be generated.

### 4.2.2 Using DTPs to calibrate the CRM

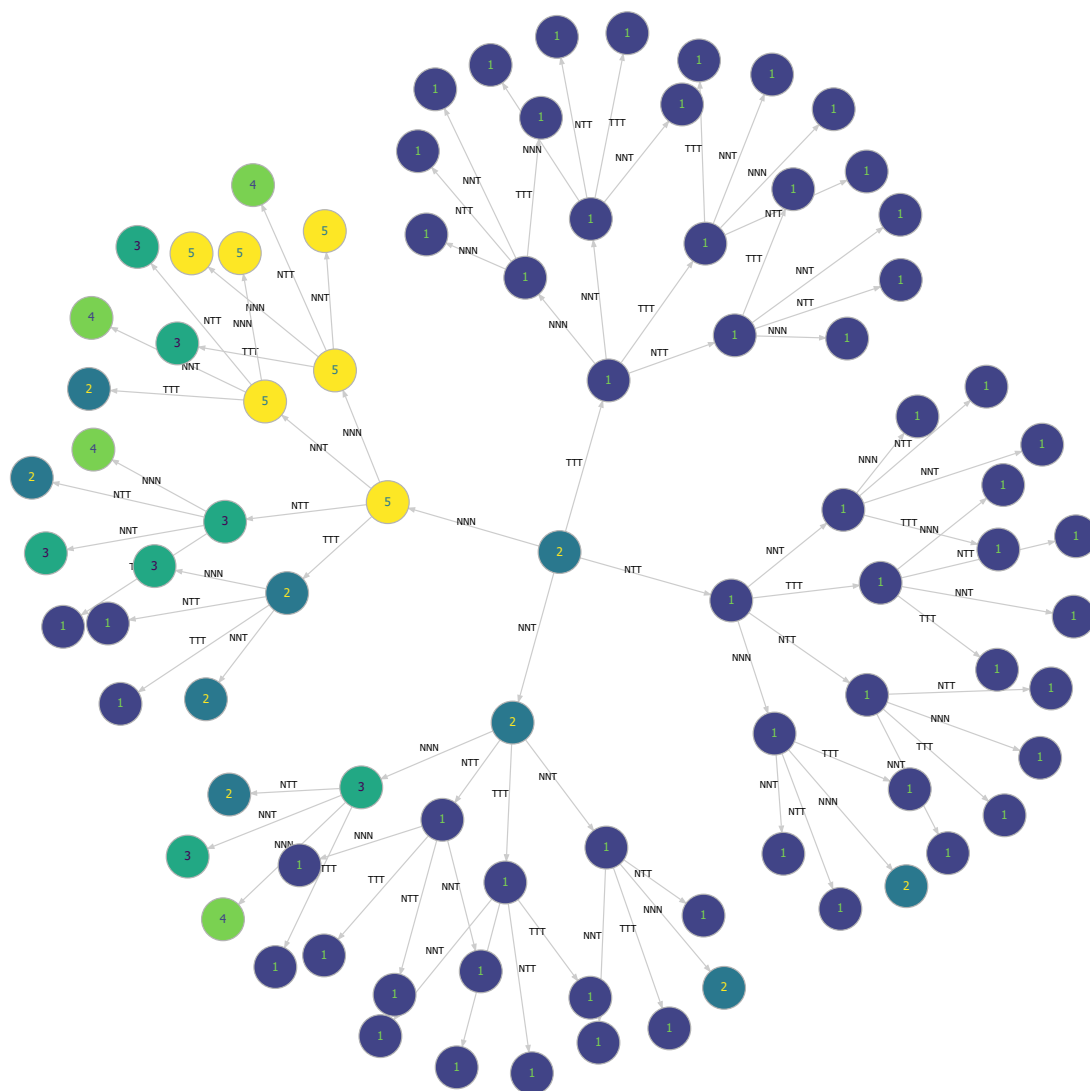
Since we have specified a sample size of 30 and cohort size of 3 that means we will have 10 cohorts and therefore 1,048,576 pathways ( $[3 + 1]^{10} = 1,048,576$ ). Patients in each cohort are considered to either experience a toxic event (T) or have no toxic event (N). For the first cohort of three patients there are four possible outcomes: all patients in experience no toxicity (NNN), one patients experience a toxic event (NNT), two patients experience a toxic event (NTT) and all three patients experience a toxic event (TTT). For the subsequent cohort the same set of 4 outcomes can be observed but then in combination with the previous cohort this creates 16 different outcomes for the first 2 cohorts (6 patients). This process is then continued for each cohort creating exponentially more pathways.

Given the impracticalities of presenting and summarising all these pathways we can instead present the pathways of the first three cohorts of patients. In this case there are only 64 potential pathways ( $[3 + 1]^3 = 64$ ). Table 4.2 lists all the potential pathways for the first three cohorts of patients. Similarly we can also represent these pathways visually using either a node plot (Figure 4.1) or a flow plot (Figure 4.2).

TABLE 4.2: Initial DTP for the first three cohorts of our example CRM.

Pathway	Cohort 1		Cohort 2		Cohort 3		Cohort 4
	Dose	Outcomes	Dose	Outcomes	Dose	Outcomes	Dose
1	2	NNN	5	NNN	5	NNN	5
2	2	NNN	5	NNN	5	NNT	5
3	2	NNN	5	NNN	5	NTT	4
4	2	NNN	5	NNN	5	TTT	3
5	2	NNN	5	NNT	5	NNN	5
6	2	NNN	5	NNT	5	NNT	4
7	2	NNN	5	NNT	5	NTT	3
8	2	NNN	5	NNT	5	TTT	2
9	2	NNN	5	NTT	3	NNN	4
10	2	NNN	5	NTT	3	NNT	3
11	2	NNN	5	NTT	3	NTT	2
12	2	NNN	5	NTT	3	TTT	1
13	2	NNN	5	TTT	2	NNN	3
14	2	NNN	5	TTT	2	NNT	2
15	2	NNN	5	TTT	2	NTT	1
16	2	NNN	5	TTT	2	TTT	1
17	2	NNT	2	NNN	3	NNN	4
18	2	NNT	2	NNN	3	NNT	3
19	2	NNT	2	NNN	3	NTT	2
20	2	NNT	2	NNN	3	TTT	1
21	2	NNT	2	NNT	1	NNN	2
22	2	NNT	2	NNT	1	NNT	1
23	2	NNT	2	NNT	1	NTT	1
24	2	NNT	2	NNT	1	TTT	1
25	2	NNT	2	NTT	1	NNN	1
26	2	NNT	2	NTT	1	NNT	1
27	2	NNT	2	NTT	1	NTT	1
28	2	NNT	2	NTT	1	TTT	1
29	2	NNT	2	TTT	1	NNN	1
30	2	NNT	2	TTT	1	NNT	1
31	2	NNT	2	TTT	1	NTT	1
32	2	NNT	2	TTT	1	TTT	1
33	2	NTT	1	NNN	1	NNN	2
34	2	NTT	1	NNN	1	NNT	1
35	2	NTT	1	NNN	1	NTT	1
36	2	NTT	1	NNN	1	TTT	1
37	2	NTT	1	NNT	1	NNN	1
38	2	NTT	1	NNT	1	NNT	1
39	2	NTT	1	NNT	1	NTT	1
40	2	NTT	1	NNT	1	TTT	1
41	2	NTT	1	NTT	1	NNN	1
42	2	NTT	1	NTT	1	NNT	1
43	2	NTT	1	NTT	1	NTT	1
44	2	NTT	1	NTT	1	TTT	1
45	2	NTT	1	TTT	1	NNN	1
46	2	NTT	1	TTT	1	NNT	1
47	2	NTT	1	TTT	1	NTT	1
48	2	NTT	1	TTT	1	TTT	1
49	2	TTT	1	NNN	1	NNN	1
50	2	TTT	1	NNN	1	NNT	1
51	2	TTT	1	NNN	1	NTT	1
52	2	TTT	1	NNN	1	TTT	1
53	2	TTT	1	NNT	1	NNN	1
54	2	TTT	1	NNT	1	NNT	1
55	2	TTT	1	NNT	1	NTT	1
56	2	TTT	1	NNT	1	TTT	1
57	2	TTT	1	NTT	1	NNN	1
58	2	TTT	1	NTT	1	NNT	1
59	2	TTT	1	NTT	1	NTT	1
60	2	TTT	1	NTT	1	TTT	1
61	2	TTT	1	TTT	1	NNN	1
62	2	TTT	1	TTT	1	NNT	1
63	2	TTT	1	TTT	1	NTT	1
64	2	TTT	1	TTT	1	TTT	1

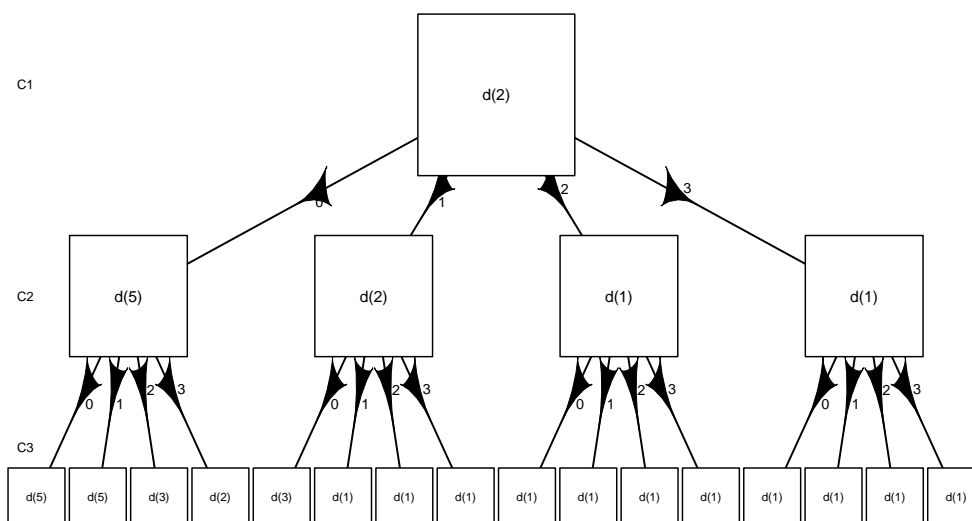
FIGURE 4.1: Initial DTP node plot for the first three cohorts of our example CRM.



From Table 4.2, looking at pathways 33-64, we can see that if there are two or more toxicities in the first cohort the CRM will always de-escalate the dose and if there are one or more toxicities in the next two cohorts it will stay at dose-level 1. We can also see from pathways 17-32 if we observe a toxicity in the first cohort we will stay at the same dose-level for the next cohort. If no toxicities occur we escalate straight to the highest dose.

Figure 4.1 also shows the same information. The central node represents the starting dose and first cohort, from here we have 4 branches showing the

FIGURE 4.2: Node plot of the initial DTP for the first three cohorts of our example CRM.



various outcomes and which dose-level is allocated to the next cohort. A quick glance at the case where each patient in the first cohort experience a DLT (TTT) we see that subsequent cohorts are all allocated to dose-level 1 regardless of their outcomes. Similarly, for when two patients from the first cohort experience DLTs (NTT) all resulting branches show that dose-level 1 would be selected except in one case where no further DLTs occur and the CRM would escalate back to the starting dose. When one DLT occurs in the first cohort (NNT), we remain at the same dose-level. Looking at these branches if one or more DLTs are experienced in the next cohorts the dose-level is de-escalated, there is only potential for escalation in the scenario where no further DLTs occur. For the case when no DLTs occur (NNN) we see the dose for the second cohort escalated to dose-level 5. At this point if the second cohort experiences 3 DLTs the CRM will de-escalate to dose-level 2, if there are only 2 DLTs the

CRM goes to dose-level 3 and one or less DLTs and the next cohort will remain at dose-level 5. The flow plot, Figure 4.2, only shows outcomes up to the third cohort but can be interpreted in a similar manner to the node plot.

In combination with operating characteristics from simulations, DTPs can be used to facilitate discussions to see if the CRM can be better calibrated and is behaving in an optimal manner. In our example here there may be a few obvious things that would concern clinicians, the first being that we skip doses when escalating and secondly that in the cases where lots of toxicity occurs recruitment continues. To remedy this we can include a rule not to skip untried doses and add a safety rule if to stop the trial if too many toxicities occur at the lowest dose.

In a Bayesian setting an appropriate method to stop early would be to test the posterior distribution for the probability of toxicity. For our example here we will stop if there is at least a 90% probability that the toxicity rate is 10% greater than the target level at the lowest dose. This can be expressed as  $P(\text{true DLT rate at } d_1 > 0.25 + 0.1 \mid \text{observed data and prior information}) > 0.9$ .

With the addition of these two rules the DTPs can be updated, and in parallel further simulations can be produced. Table 4.3 shows the pathways for the first three cohorts. The node and flow plots were also updated, Figure 4.3 and 4.4 respectively. Since we included a rule to stop in the case of excess toxicity we see a number of pathways terminate early so overall there are less pathways compared to the initial set that were produced. Here we see six different branches where it is recommended that the trial stop early (pathways 32, 44, 45, 53, 54, 55 Table 4.3). This can also be seen in Figure 4.3, we can also see three of these nodes recommend stopping before recruiting a third cohort. Using the flow plot, Figure 4.4, we can clearly see that stopping is suggested when five out of the first six patients experience a DLT. Also, escalation of doses no longer skips dose-levels. With these new rules we observe that if there are no

DLTs in the first cohort the dose for the next cohort is dose-level 3 and not 5. We still observe that one toxicity in the first cohort leads to recruiting the next cohort at that same dose-level and with two or more toxicities de-escalation occurs.

TABLE 4.3: Updated DTPs for the first three cohorts of our example CRM with additional rules.

Pathway	Cohort 1		Cohort 2		Cohort 3		Cohort 4
	Dose	Outcomes	Dose	Outcomes	Dose	Outcomes	Dose
1	2	NNN	3	NNN	4	NNN	5
2	2	NNN	3	NNN	4	NNT	5
3	2	NNN	3	NNN	4	NTT	4
4	2	NNN	3	NNN	4	TTT	3
5	2	NNN	3	NNT	3	NNN	4
6	2	NNN	3	NNT	3	NNT	3
7	2	NNN	3	NNT	3	NTT	2
8	2	NNN	3	NNT	3	TTT	1
9	2	NNN	3	NTT	2	NNN	3
10	2	NNN	3	NTT	2	NNT	2
11	2	NNN	3	NTT	2	NTT	1
12	2	NNN	3	NTT	2	TTT	1
13	2	NNN	3	TTT	1	NNN	2
14	2	NNN	3	TTT	1	NNT	1
15	2	NNN	3	TTT	1	NTT	1
16	2	NNN	3	TTT	1	TTT	1
17	2	NNT	2	NNN	3	NNN	4
18	2	NNT	2	NNN	3	NNT	3
19	2	NNT	2	NNN	3	NTT	2
20	2	NNT	2	NNN	3	TTT	1
21	2	NNT	2	NNT	1	NNN	2
22	2	NNT	2	NNT	1	NNT	1
23	2	NNT	2	NNT	1	NTT	1
24	2	NNT	2	NNT	1	TTT	1
25	2	NNT	2	NTT	1	NNN	1
26	2	NNT	2	NTT	1	NNT	1
27	2	NNT	2	NTT	1	NTT	1
28	2	NNT	2	NTT	1	TTT	1
29	2	NNT	2	TTT	1	NNN	1
30	2	NNT	2	TTT	1	NNT	1
31	2	NNT	2	TTT	1	NTT	1
32	2	NNT	2	TTT	1	TTT	STOP
33	2	NTT	1	NNN	1	NNN	2
34	2	NTT	1	NNN	1	NNT	1
35	2	NTT	1	NNN	1	NTT	1
36	2	NTT	1	NNN	1	TTT	1
37	2	NTT	1	NNT	1	NNN	1
38	2	NTT	1	NNT	1	NNT	1
39	2	NTT	1	NNT	1	NTT	1
40	2	NTT	1	NNT	1	TTT	1
41	2	NTT	1	NTT	1	NNN	1
42	2	NTT	1	NTT	1	NNT	1
43	2	NTT	1	NTT	1	NTT	1
44	2	NTT	1	NTT	1	TTT	STOP
45	2	NTT	1	TTT	STOP	NA	STOP
46	2	TTT	1	NNN	1	NNN	1
47	2	TTT	1	NNN	1	NNT	1
48	2	TTT	1	NNN	1	NTT	1
49	2	TTT	1	NNN	1	TTT	1
50	2	TTT	1	NNT	1	NNN	1
51	2	TTT	1	NNT	1	NNT	1
52	2	TTT	1	NNT	1	NTT	1
53	2	TTT	1	NNT	1	TTT	STOP
54	2	TTT	1	NTT	STOP	NA	STOP
55	2	TTT	1	TTT	STOP	NA	STOP

At this stage, further discussions could be held about the updated DTPs and simulations. Here there, may be more subtle points to discuss such as the

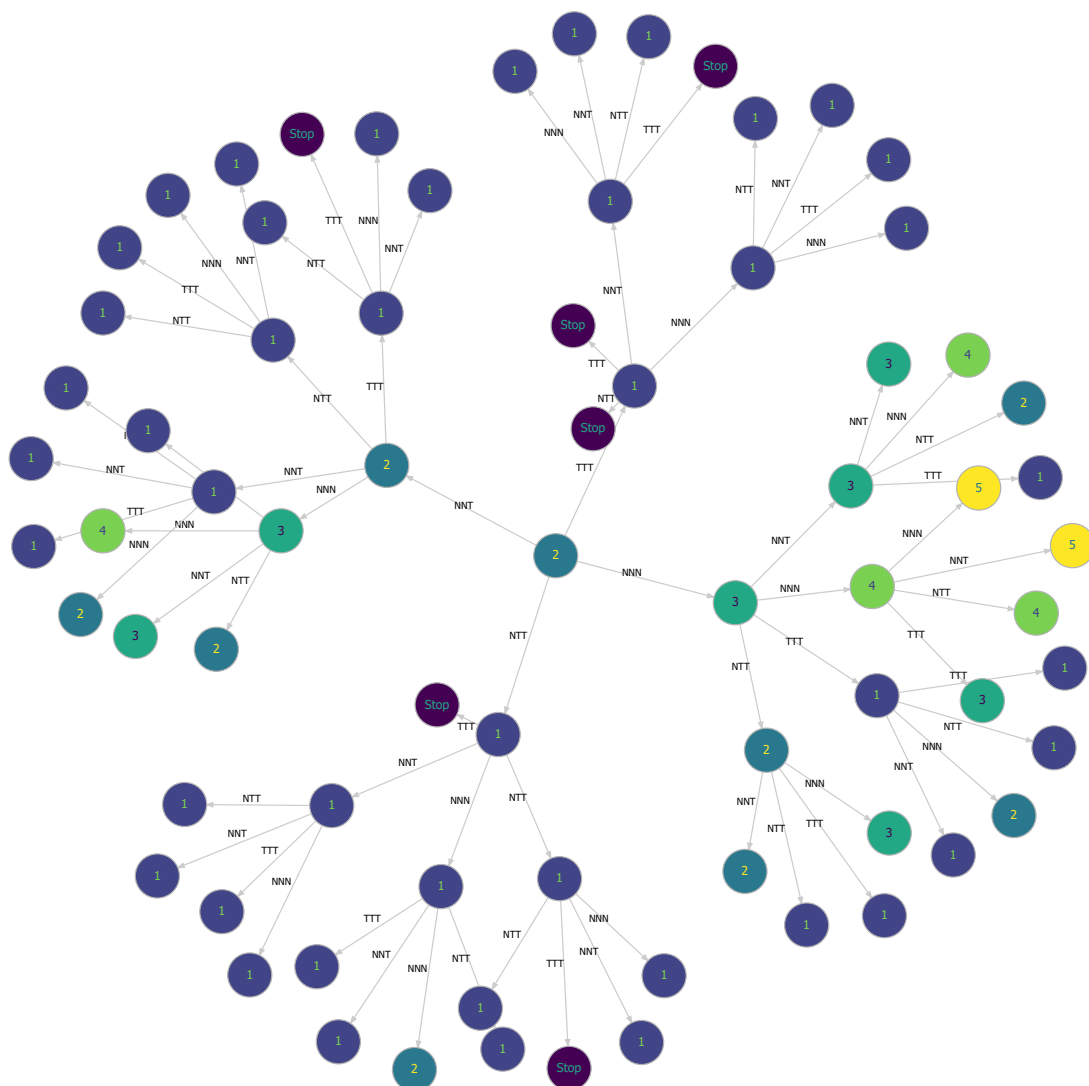
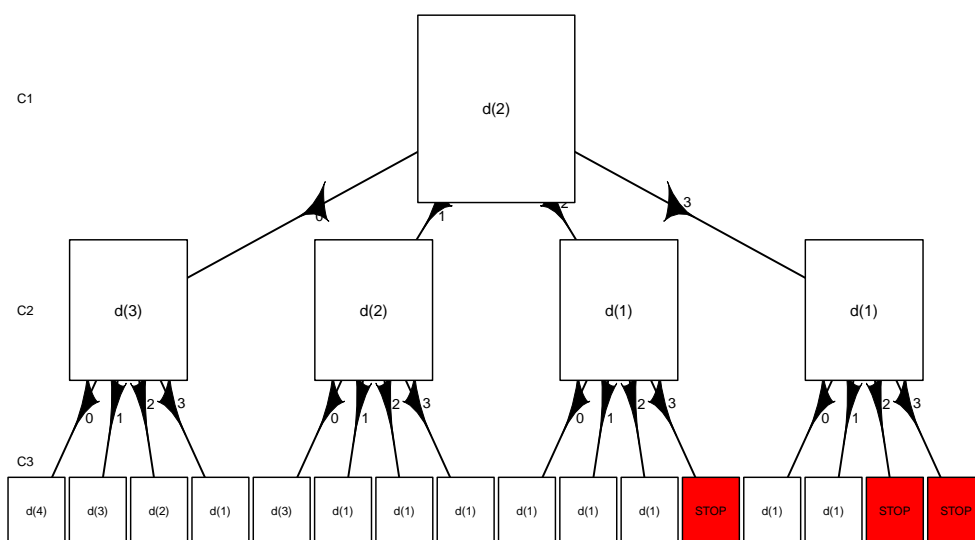
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FIGURE 4.4: Node plot of the updated DTP for the first three cohorts of our example CRM with additional rules.



observed in the previous cohort. This property limits the risk of unnecessarily exposing patients to toxic doses whilst also ensuring patients get treated at a reasonable dose within the safety limit [45]. This became an issue due to the rule we enforced not to skip doses in escalation, the previous design without this rule was in fact coherent. Further rules could be added to ensure the design remains coherent such that escalation will only take place if the previous cohort experience no DLTs likewise, de-escalation will only occur if the previous cohort did experience DLTs.

Here we have highlighted the ways in which DTPs can be utilised during the initial stages of setting up a trial. Due to our example there were some obvious changes that could be implemented into our suggested design. However, this was just to illustrate what the pathways look like and how they can be used to facilitate discussions with the relevant clinicians and the trials team.



Although we just looked at DTPs any changes being made to the design should also take into account results from the simulations. CRM designs may not be intuitively understood by clinicians but DTPs should help make them more accessible. Next we will look at how DTPs can be used during a trial.

### **4.2.3 DTPs as an analysis tool**



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