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Time-Based Bayesian Optimal Interval (TITE-BOIN) Design Algorithm Performance under Weibull Distribution on Simulated Phase I Clinical Trial Data

by

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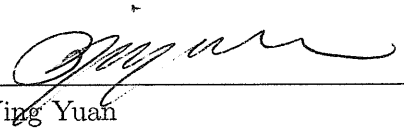

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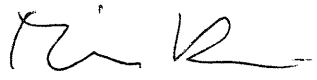

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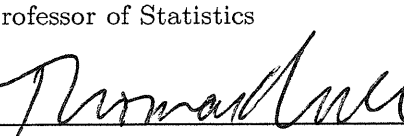

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ABSTRACT

Time-Based Bayesian Optimal Interval (TITE-BOIN) Design Algorithm
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In phase I clinical trials, the goal is to effectively treat the patient while minimizing the chance of exposing them to excessively toxic doses of a new drug. In order to choose the correct dose, we use an adaptive dose-finding design, the Bayesian optimal interval design (BOIN), to aid in this selection. Here, we propose an evaluation of the Bayesian optimal interval design with patient accrual given under the Weibull and uniform distribution, comparing it to a time-based algorithm of the BOIN; Time to Event BOIN (TITE-BOIN). Simulations show that under the Weibull distribution, standard BOIN surpasses the TITE-BOIN design in terms of recommendation of maximum tolerated dose and allocation of data. In addition, both designs under the Weibull perform better than the uniform distribution when selecting a dose. Further study of the effects of the Weibull parameters on the BOIN design and the duration of trial under the Weibull is to be considered.

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Chapter 1

Introduction

In phase I clinical trials, there are numerous designs that have been recommended to identify the dose of a new drug with a dose-limiting toxicity probability. This dose is close to a target toxicity rate, commonly referred to as the maximum tolerated dose (MTD). Among these designs, we have 3+3 design [2] [3], the continual reassessment method (CRM) [4], and others, each having been provided with intensive reviews of dose-finding methods for phase I clinical trials. The Bayesian Optimal Interval design is a recently developed method whose practicality and function was created with the phase I clinical researcher in mind. The design's purpose is to determine the maximum tolerated dose that effectively treats the patient and minimizes the chance of exposing the cohort to subtherapeutic or overly toxic doses of the drug in question. The algorithm-based process of the design allows for easy implementation in practice and has excellent operating characteristics. Performance of the BOIN is comparable to that of the 3+3 and CRM, but has a lower risk of patients being assigned a subtherapeutic or overly toxic dose. Building upon this, we aim to develop an algorithm that not only applies a Weibull distribution as a measure for the toxicity probability, but also incorporates a time factor, such that we are able to determine the duration of such a trial.

In terms of real world application, this design takes Bayesian interval methodology and applies it in a way that locates the MTD within a reasonable range of our target toxicity rate, while keeping the number of patients exposed to subtherapeutic

or overly toxic doses at a minimum. Our main motivation behind development of the algorithm focuses on easy functionality and understanding by clinicians and researchers of different practices.

1.1 Motivation

Dose-finding algorithms for phase I clinical trials have provided researchers with a method of determining the *Maximum Tolerated Dose* a patient should be provided without causing harm. Between the 3+3 Design, *continual reassessment method* (CRM), and the *Bayesian Optimal Interval* (BOIN) Design, it is practical to select the method that provides the MTD for dose selection without stopping the trial. BOIN currently does just this under a uniform distribution for observed toxicity, as do the previously mentioned methods.

Suppose, we were to believe the level of toxicity was to be observed as a Weibull distribution; how then would this affect the MTD to be given to a cohort or group of cohorts during a typical phase I clinical trial? Would this predicted distribution affect the duration of our trial? These are the questions that we hope to answer with this study.

We begin our study by describing what the 3+3 and continual reassessment are in order to have a better understanding of what our model will be doing. Focus will then be placed on what the BOIN interval design is and how it works. We will then go into detail on the selection of the parameters of the Weibull distribution. From this point, we proceed to discuss how the accrual rate of patients affects the duration of the trial, and if the rate and distribution in turn affect the results of the trial in terms of its duration.

Chapter 2

Phase I Clinical Trial Designs

Phase I clinical trials primarily focus on the testing of a new drug or treatment on a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. Designs currently in use are the 3+3 and Continual Reassessment Method, among numerous other designs. These designs will be briefly mentioned in this chapter to provide the reader with an idea as to what this study seeks to accomplish by using the Bayesian Optimal Interval Design.

The following designs can be studied more deeply in Tourneau, Lee, and Siu's paper on Dose Escalation Methods on Phase I Cancer Clinical Trials [5].

2.1 3+3 Design

The most prevalent of the Phase I cancer clinical trial designs, the 3+3 is a rule-based design that is carried out with a cohort of three patients [2]. The first cohort is provided treatment at a starting dose that is determined to be safe based on data collected prior to the trial. Subsequent cohorts are then treated at fixed increasing dose levels that were also determined prior to the trial. Should any of the three patients in the fist cohort not experience a dose-limiting toxicity, the next three patients are to be treated at the next higher dose level. If one of the patients dose experience a dose-limiting toxicity, the following three patients will be treated at the same dose level. This process of escalation continues until until at least two of patients

among a cohort of three to six patients experiences dose limiting toxicities.

In addition to being both a simple to implement and safe design, the ability to accrue three patients per dose level provides additional information about the patient variability in terms of how their bodies responds to a drug. This, however, does not make up for the large proportion of patients treated at low, possibly subtherapeutic, doses as a result of the high number of escalation steps, which further leads to few patients actually receiving doses at or near the recommended dose for a trial. A method better suited for handling such a case is the continual reassessment method.

2.2 Continual Reassessment Method

Known as the first Bayesian model-based method proposed for use in phase I clinical trial designs, the continual reassessment method makes use of a θ estimate which is derived from information provided by those who have familiarity with the preclinical data or have experience with similar drugs if any exist [4]. Providing guidance about dose escalation, it should be noted that the initial estimate may not be the most accurate. In the continual reassessment method [4], all patients are treated at the dose perceived to be closest to the MTD, which corresponds to the dose at the target dose-limiting toxicity level. Updating the estimate of the probability of encountering a dose-limiting toxicity for each new patient who enter the study at any dose level, the method continues until a prespecified condition is met, resulting in the trial being stopped. Among the various stopping rules, the most trivial one requires that the trial be stopped when six patients are assigned the same dose. A trial can also be stopped if a certain precision in the probability of dose-limiting toxicity at the estimated MTD level is achieved. This method allows for multiple dose escalation and de-escalations.

A major disadvantage of this method is that if the prespecified dose model is incorrect, this puts patients at risk of being exposed to overly toxic doses of a drug. The BOIN design seeks to provide a method which lowers such a risk for patients in a given phase I clinical trial.

2.3 Bayesian Optimal Interval Design

The Bayesian optimal interval (BOIN) design proposed by Liu and Yuan [6] is a rising new method for finding the MTD of a drug in phase I clinical trials. BOIN design seeks to find the MTD while also minimizing the probability of assigning a patient or group of patients a subtherapeutic or overly toxic dose.

Under BOIN, a new class of phase I trial designs known as interval design is being used. The idea behind the design is to determine how to transition between dose levels based on previous observations. More formally, the interval design is one in which the dose transition is defined by the approximate location of the observed toxicity rate at the current dose with respect to a pre-specified toxicity tolerance interval [7]. This design proves beneficial when determining whether to escalate, deescalate, or retain the dose of a new drug in a phase I trial, and can be comparable to additional designs, such as the 3+3 and CRM.

Let us consider phase I clinical trials as a form of decision-making, where the choices are as follows: escalate, deescalate, or retain the current drug dosage for a patient. To ensure that the drug is being assigned at a level that provides the desired results, we treat each of our decisions such that we escalate the drug dose when the

current dose is under the MTD to avoid treating at subtherapeutic levels; deescalate when the current dose is the above the MTD in order to avoid giving the patient an overly toxic dose; and retain the same dose when the current dose is equal to or close to the MTD [6]. In practice, however, this is usually not the case since we do not have knowledge as to whether the current dose is lower, higher, or equivalent to the MTD. At the same time, we must be able to make an inference based on the data collected from patients currently enrolled in the trial, so that a decision on dose can be assigned for the next cohort. Accompanied by randomly observed data and small sample size, the inferences made based on the information provided is often incorrect, resulting in a disruption in ethics. A phase I clinical trial often leads to a patient, or group of patients, being improperly assigned a dose level, i.e. a patient receives a lower dose of a drug, when in reality they either needed a higher dose or required no escalation at all. This, in turn, leads to the desire for a design which minimizes the chance of such an error in the decision process occurring. It is for these reasons that the BOIN design was created.

Chapter 3

Bayesian Optimal Interval Design

3.1 Method

By applying the Bayesian Optimal Interval design boundary conditions with a simulated observed toxicity under a weibull distribution, the algorithm will provide results similar to that of the BOIN under the uniform distribution. The focus of the algorithm is to get the best results for the MTD with the lowest risk of poor allocation possible. Patient entry into the study will be modeled as a Poisson process. The times of entry will be recorded so as to determine how long such a trial would take under desired conditions.

Some of the main factors to keep in mind are the accrual rate, the assessment period, and the number of observed toxicities that occur beyond the halfway point of the study. For the sake of this study, we will focus on a simulation of the algorithm under fixed "true" toxicities as seen under varying accrual rates of patients.

3.2 Interval Design

Interval designs are generally described as follows with the assumption of J prespecified doses and we allow ϕ to denote the target toxicity rate specified by physicians:

1. Patients in the first cohort are treated at the lowest dose level.

2. At the current dose level j, assume that a total (or the cumulative number) of n_j patients have been treated, and m_j of them have experienced toxicity. Let $\hat{p}_j = m_j/n_j$ denote the observed toxicity rate at dose level j, and $\lambda_{1j}(n_j, \phi)$ and $\lambda_{2j}(n_j, \phi)$ denote the pre-specified lower and upper (or dose escalation and deescalation) boundaries of the interval respectively, with $0 \leq \lambda_{1j}(n_j, \phi) < \lambda_{2j}(n_j, \phi) \leq 1$. To assign a dose to the next cohort of patients,

   - if $\hat{p}_j \leq \lambda_{1j}(n_j, \phi)$, we escalate the dose level to j+1;
   - if $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$, we deescalate the dose level to j-1;
   - otherwise, i.e. $\lambda_{1j}(n_j, \phi) < p_j < \lambda_{2j}(n_j, \phi)$, we retain the same dose level j.

   To ensure that the dose levels of the treatment always remain with the pre-specified dose range, the dose escalation/deescalation rule requires some adjustments when j is at the lowest or highest level. That is, if j=1 and $\hat{p}_j \geq \lambda_{2j}(n_j, \phi)$ or j=J and $\hat{p}_j \leq \lambda_{1j}(n_j, \phi)$, the dose remains at the same level, j.

3. This is continued until the maximum sample size is reached or the trial is terminated due to excessive toxicity, i.e. where the boundary condition for observed toxicity has been reached or exceeded [6].

What allows BOIN to stand apart from the other designs is its dependence on both the dose level j and the number of patients being treated, n_j, while the other methods assume the interval boundaries are independent of j and n_j.

Within the algorithm in question, special attention is given to the boundary conditions that classify how the dose-escalation/deescalation decision for a drug takes

place. In addition, the toxicity probability seen by the Weibull distribution will be discussed in further detail.

3.3 Late Onset Toxicity

Perhaps the more difficult concept of the design is the understanding of how the observation of late-onset toxicity works and how it affects the results of the trials. Here, we briefly discuss the concept of this non-ignorable missing data to aid in understanding of how it applies in this study. The following image depicts how, given a cohort of patients, the decision of what dose of a drug in question to give a patient or group of patients would be decided. Of the patients being treated, only two patients have experienced a toxicity. With this in mind, the dose of the drug to give to a patient or group of patients will be selected based on the results of those

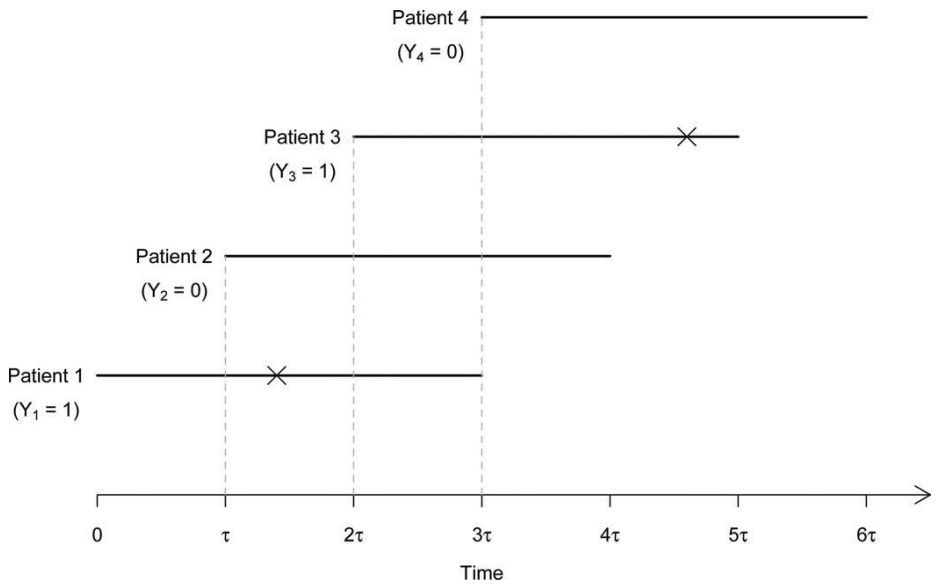

Figure 3.1 : Illustration of missing toxicity outcomes under fast accrual. For each patient, the horizontal line segment represents the follow-up, on which toxicity is indicated by a cross [1].

being treated. Note, the two patients that did not observe any toxicity cannot just be ignored when making this decision, and also must be considered when making a choice in dose. It is at this point that the BOIN design aids in the decision.

To further elaborate upon this, let us consider what it means to have non-ignorable missing data. Referring back to our image, consider the patient inter-arrival time τ, which is shorter than the assessment period T. In this scenario, if a dose were to be assigned to a newly accrued patient, i.e. patient 4 at time 3τ, some of the patients who have entered the trial, i.e. patients 2 and 3, may have partially been followed, but their toxicity outcomes may not be available. Let t_i denote the time to toxicity for the ith subject. Subjects who do not experience toxicity during the trial have a set $t_i = \infty$. Let u_i $(0 \leq u_i \leq T_i)$ denote the actual follow-up time for subject i, and let $M_i(u_i)$ be the missing data indicator for Y_i at the moment a decision for dose assignment must be made. It then follows that:

$$M_i(u_i) = \begin{cases} 1, & \text{if } t_i > u_i \text{ and } u_i < T. \\ 0, & \text{if } t_i \leq u_i \text{ or } u_i = T. \end{cases}$$

Under this missing data mechanism, we then treat the missing data induced by late-onset toxicity as non-ignorable with $Pr(M_i = 1|Y_i = 0) > Pr(M_i = 1|Y_i = 1)$ [1]. What this means is that this induced missing data is informative as a result of the probability of missingness of Y_i depending on the underlying time to toxicity, and thus implicitly depends on the value of Y_i itself. Further examination of this mechanism can be studied in Liu, Yin, and Yuan's Bayesian Data Augmentation Dose Finding article [1].

Chapter 4

Weibull Distribution

The Weibull distribution has been used in a variety of reliability and life data, or survival, analysis. Using this distribution allows for numerous life behavior models depending on the selection of the parameters. These parameters are seen to have much affect on the distribution characteristics of the Weibull; from the shape of the density curve to the reliability and failure rate.

In the BOIN setting, we will choose our scale and shape parameters such that the output of the cumulative distribution function at a given assessment period will be the probability of toxicity occurrence.

4.1 Parameter Selection

To determine what values to use for our scale and shape parameter, we will be using a similar methodology as seen in [1]. With the time to toxicity under the Weibull, we desire to control the percent of toxicity events, denoted as the parameter δ, that occur in the latter half of the assessment period (T/2,T). That is to say at each dose level, the scale and shape parameters of the Weibull distribution were chosen such that

1. the cumulative distribution function at the end of the follow-up time T would be the toxicity probability of that dose; and

2. among all the toxicities that occurred in (0,T), δ% of them would occur in

(T/2,T), the latter half of the assessment period.

For the duration of the study the assessment period will remain fixed at T = 3 months. Note that the scale and shape parameter of the distribution can be selected differently under each dose, as seen in Liu, Yin, and Yuan [1]. However, for the duration of the trial, the shape parameter will be fixed at 4 with an allowed variation of the scale parameter either 1 and .4 as seen in Cheung and Chapell [8].

Chapter 5

Numerical Studies

5.1 Simulation

The simulation will be run with the following conditions: each trial will be run with a sample size of 36, an assessment period of 3 months and an accrual rate of 5 patients every 30 days. Similar to Cheung and Chapell [8], the shape parameter of the Weibull will be fixed at 4 and the scaling parameter will be selected such that the resulting cumulative distribution displays the probability of observed toxicity. There will be 10 scenarios using "true" toxicity probabilities of five doses to aid in the trials. Results are to be compared to those of the BOIN model under the Uniform and Weibull distribution.

Chapter 6

Results

The percentages of the recommended doses at the Maximum Tolerated Dose are shown in the tables 8.1-8.5 with their respective scenarios.

The BOIN based algorithm applied with Weibull distribution seems to be fairly comparable to that of the classic BOIN design. With a fixed shape and scale parameter, the results of the two designs are almost similar. However, when viewing the results of the algorithm, we see there is a problem when determining what dose to provide to the following cohorts. This situation may very well result from the allocation of the data within the algorithm, implying that the selection options of escalation/deescalation are in need of revision. In addition, it has been seen through further simulations that the shape, scale, and sample size do have an effect on the results of both algorithms.

Given the results, the study could extensively go on in order to determine the best choice for these three variables when handling the output. Comparing this algorithm to the BOIN method, BOIN is seen to show remarkable results under the Weibull.

Table 6.1 : Operating Characteristics of BOIN and TITE-BOIN design under pre-specified dose toxicity scenario 1-2. Target toxicity rate of .30

Design		d_1	d_2	d_3	d_4	d_5	Risk of Poor Allocation, %	Risk of high Toxicity, %
Scenario 1	Pr(Toxicity)	.3	.45	.5	.6	.7		
Uniform	BOIN	**64.6**	14.6	2.8	0.5	0.0	8.9	51.1
	# patients	**18.5**	6.6	1.3	0.2	0.0		
	TITE-BOIN	**47.1**	2.3	0.9	0.0	0.0	32.9	77.2
	# patients	**15.6**	11.0	2.9	0.4	0.0		
Weibull	BOIN	**86.2**	0.0	0.0	0.0	0.0	1.9	46.4
	# patients	**24.0**	3.2	0.0	0.0	0.0		
	TITE-BOIN	**23.2**	0.0	0.0	0.0	0.0	49.4	92.7
	# patients	**14.8**	21.1	0.1	0.0	0.0		
Scenario 2	Pr(Toxicity)	0.15	0.3	0.45	0.5	0.6		
Uniform	BOIN	23.9	**56.2**	17.6	1.5	0.0	12.5	26.2
	# patients	10.1	**13.3**	5.5	0.8	0.1		
	TITE-BOIN	**32.3**	14.4	1.3	0.2	0.0	36.1	55.6
	# patients	**6.4**	13.0	8.5	2.0	0.1		
Weibull	BOIN	11.9	**87.8**	0.3	0.0	0.0	3.0	23.7
	# patients	7.5	**19.5**	3.0	0.0	0.0		
	TITE-BOIN	**24.1**	0.0	0.0	0.0	0.0	49.3	85.0
	# patients	**3.3**	14.3	18.3	0.1	0.0		

Chapter 7

Discussion

7.1 Data Allocation

It should be noted that the results of the simulation occurred due to a variety of reasons, i.e. the dose that is given to a cohort at the start of the trial, the corresponding shape and scale parameters that align with the aforementioned parameters, the sample size of the trials, the dose that is given at the start of the trial, and so on.

Perhaps the most difficult part of running the simulations was ensuring that the correct estimates were being used for each dose being given at the start of the trial, i.e. currdose = 1,....,6 and shape = ... and scale = ... Even with the suggested estimates of Cheung and Chappell [8], output was not as desired for the algorithm.

To make sure the seen results permit a correct allocation of the data, the estimates that allowed for the cumulative distribution of the Weibull to be the toxicity probability under each dose, respectively had to be computed properly. Seeing that not all clinicians are going to want to compute the estimates that are suitable for the drug doses they are testing, the Weibull may not be the best distribution, depending on the true toxicities provided. That is to say, until further study has been done such that there are universally known estimates that can be used under this distribution given the starting dose of a trial. However, if there's a common toxicity by which the estimates apply, then this shouldn't be a major problem in the long run.

When the improper estimate is used, large amounts of poor data allocation is seen

along with high probability of toxicity in the trial. Again, this most likely relates to the estimates which are chosen for each starting dose in our trials.

7.2 Early Stopping

Another concern is the percentage of early stopping that took place within both the BOIN and the TITE-BOIN algorithm. Allowing the shape and scale parameters to remain fixed for the trials shows that it is a necessity to have these values changed depending on the starting dose of the trial. Here, the starting dose of each trial was always the first. Given a different starting dose and the qualifying shape and scale parameter of the Weibull, the results of the BOIN and TITE-BOIN could yield even better allocation, toxicity probability, and average duration of trials.

7.3 Time Allocation

Another concern is the allocation of the duration of the trials. A majority of the trial duration times were output as an NA, which isn't reasonable in terms of real world application. It is more desirable to have the duration of each trial to exist along the scope of our assessment period, such that we get accurate data for determining how long the trials would last overall.

Knowing this time would allow clinicians to properly prepare and anticipate the time it would potentially take to measure the results.

Given what we know and what we would like to know about the data, it is possible that there's a better means of computing the trial duration for this study or any other study. In addition, we should take into account that the distribution of our observed toxicities can also play a role in the length of time to complete the phase I clinical trial.

Determining the amount of time each of these trials would take proved to be a bit more challenging than previously anticipated. There are a number of methods to determine this value separate of our BOIN design, however, the goal here was to compute this value based on the accrual rate of patients into the trial. Among the methods identified, both used a Poisson process, one outputting the time in days, the other in years. The use of this time-based function would be of significant interest when wanting to predict how long a trial would take under this design. In this study, the current TITE-BOIN design outputs the time at a rather large span of approximately 10 years under the current parameters used. Further work and reading on this portion of the algorithm are to be completed upon further reevaluation of this topic.

Chapter 8

Conclusion

The goal of the TITE-BOIN design was to develop an algorithm comparable to the BOIN model under a Weibull distribution. Working on the development of a time-oriented BOIN design under the Weibull has led to unexpected results. By seeking to develop this algorithm, it was discovered that the Weibull distribution could be a more beneficial distribution to use on an already effective BOIN design. The Weibull displayed reasonable and comparable results to a uniformly distributed assumption on patient accrual, having effectively lower poor data allocation than that of the standard uniform distribution. Each recommended dose provided by the BOIN design was equivalent, with the design under the Weibull having the higher selection percentage for a recommended dose.

Intensive research is to be considered for the selection of the shape and scale parameter of the Weibull as well as the effects of sample size, accrual rate, and other parameters for both designs used in this study. One of the major shortcomings of both the TITE-BOIN algorithm and potentially the BOIN is the duration a phase I clinical trial would take under the assumption of a Weibull distribution. Although selection of the MTD under the BOIN provides desirable results, the time in which it would take seems unreasonable. Overall, the algorithm is in need of improvement, but the BOIN design is seen to be one that should be used more in phase I trials.

Chapter 9

Supplementary Material

The following are additional tables from the results:

Table 9.1 : Operating Characteristics of BOIN and TITE-BOIN design under pre-specified dose toxicity scenario 3. Target toxicity rate of .30

Design		d_1	d_2	d_3	d_4	d_5	Risk of Poor Allocation, %	Risk of High Probability, %
Scenario 3	Pr(Toxicity)	.1	.15	.3	0.45	0.5		
Uniform	BOIN	1.6	**21.6**	11.1	19.6	1.6	17.6	9.5
	# patients	4.9	**8.5**	11.1	4.7	0.9		
	TITE-BOIN	7.9	**23.8**	15.4	2.7	0.3	37.6	32.0
	# patients	4.5	**6.1**	10.6	7.0	1.7		
Weibull	BOIN	0.0	10.1	**89.6**	0.3	0.0	1.8	10.8
	# patients	3.1	6.5	**17.4**	3.0	0.0		
	TITE-BOIN	0.1	**26.7**	0.0	0.0	0.0	50.4	77.1
	# patients	3.0	**3.2**	13.4	16.3	0.0		

Table 9.2 : Operating Characteristics of BOIN and TITE-BOIN design under pre-specified dose toxicity scenario 4. Target toxicity rate of .30

Design		d_1	d_2	d_3	d_4	d_5	Risk of Poor Allocation, %	Risk of High Probability, %
Scenario 4	Pr(Toxicity)	.1	.15	.2	.3	.45		
Uniform	BOIN	1.6	8.4	29.3	**42.2**	18.3		
	# patients	4.8	6.4	8.0	**7.1**	3.6	37.2	3.0
	TITE-BOIN	8.5	10.3	**20.1**	16.4	7.3	50.3	10.1
	# patients	4.5	5.9	**6.9**	7.5	5.2		
Weibull	BOIN	0.0	0.0	10.1	**89.5**	0.4	2.4	3.1
	# patients	3.1	3.2	6.4	**14.5**	2.8		
	TITE-BOIN	0.0	0.7	**25.3**	0.0	0.0	47.9	70.4
	# patients	3.0	3.2	**3.9**	12.5	13.41		

Table 9.3 : Operating Characteristics of BOIN and TITE-BOIN design under pre-specified dose toxicity scenario 5. Target toxicity rate of .30

Design		d_1	d_2	d_3	d_4	d_5	Risk of Poor Allocation, %	Risk of High Toxicity, %
Scenario 5	Pr(Toxicity)	.1	.15	.20	.25	.3		
Uniform	BOIN	1.6	8.4	22.3	28.3	**39.2**	53.6	1.4
	# patients	4.8	6.4	7.3	6.0	**5.5**		
	TITE-BOIN	8.2	10.0	13.8	15.7	**27.3**	51.4	2.9
	# patients	4.5	5.9	6.8	6.2	**6.5**		
Weibull	BOIN	0.0	0.0	1.1	20.8	**78.1**	12.7	0.0
	# patients	3.1	3.2	4.2	7.0	**12.5**		
	TITE-BOIN	0.1	0.3	5.0	27.3	**57.5**	6.3	2.3
	# patients	3.0	3.2	3.8	6.0	**20.1**		

Table 9.4 : Operating Characteristics of BOIN and TITE-BOIN design under pre-specified dose toxicity scenario 1-2. Target toxicity rate of .25

Design		d_1	d_2	d_3	d_4	d_5	Risk of Poor Allocation, %	Risk of High Toxicity, %
Scenario 1	Pr(Toxicity)	.02	.05	.10	.25	.3		
Uniform	BOIN	0.0	1.6	24.0	**46.3**	28.1	23.5	2.0
	# patients	3.8	5.1	8.4	**8.0**	4.6		
	TITE-BOIN	2.1	8.8	29.2	**26.3**	21.4	53.6	13.2
	# patients	3.2	3.8	5.8	**11.7**	11.5		
Weibull	BOIN	0.0	0.0	1.1	37.7	**61.2**	30.6	0.3
	# patients	3.0	3.0	5.4	11.5	**13.1**		
	TITE-BOIN	0.0	0.5	**29.8**	0.4	0.2	26.5	80.2
	# patients	3.0	3.0	**3.2**	19.9	6.9		
Scenario 2	Pr(Toxicity)	0.08	0.25	0.3	0.4	0.52		
Uniform	BOIN	15.3	**52.0**	25.2	6.7	0.8	13.6	21.6
	# patients	10.3	**11.9**	5.7	1.9	0.3		
	TITE-BOIN	**43.3**	18.7	6.8	1.8	0.1	47.4	50.6
	# patients	**5.2**	15.4	8.9	4.7	1.8		
Weibull	BOIN	1.2	35.1	**62.0**	1.7	0.0	28.6	18.2
	# patients	5.7	13.4	**13.8**	3.0	0.1		
	TITE-BOIN	**30.6**	0.0	0.0	0.0	0.0	28.5	93.6
	# patients	**3.2**	23.5	8.9	0.4	0.0		

Table 9.5 : Operating Characteristics of BOIN and TITE-BOIN design under pre-specified dose toxicity scenario 3-4. Target toxicity rate of .30

Design		d_1	d_2	d_3	d_4	d_5	Risk of Poor Allocation, %	Risk of High Toxicity, %
Scenario 3	Pr(Toxicity)	.05	.06	.08	0.11	0.25		
Uniform	BOIN	0.0	1.9	5.1	27.6	**65.4**	28.6	0.2
	# patients	4.4	4.8	5.4	6.9	**8.6**		
	TITE-BOIN	1.9	3.8	10.0	32.2	**48.1**	15.2	3.3
	# patients	3.8	4.1	4.5	6.0	**17.7**		
Weibull	BOIN	0.0	0.0	0.0	1.9	**98.1**	1.1	0.0
	# patients	3.0	3.0	3.1	5.7	**21.2**		
	TITE-BOIN	0.0	0.1	1.6	**41.4**	11.6	0.1	44.6
	# patients	3.0	3.0	3.1	**3.4**	23.6		
Scenario 4	Pr(Toxicity)	.25	.3	.38	.45	.56		
Uniform	BOIN	**52.2**	24.9	8.6	1.6	0.0	11.9	53.1
	# patients	**17.5**	7.0	2.5	0.6	0.1		
	TITE-BOIN	**57.1**	10.5	2.0	0.2	0.0	48.8	69.3
	# patients	**17.4**	10.1	6.3	1.6	0.6		
Weibull	BOIN	33.9	**61.7**	3.4	0.1	0.0	28.4	35.6
	# patients	15.9	**15.8**	3.8	0.3	0.0		
	TITE-BOIN	**28.2**	0.0	0.0	0.0	0.0	24.7	98.6
	# patients	**26.9**	8.6	0.5	0.0	0.0		

Table 9.6 : Operating Characteristics of BOIN and TITE-BOIN design under pre-specified dose toxicity scenario 5. Target toxicity rate of .30

Design		d_1	d_2	d_3	d_4	d_5	Risk of Poor Allocation, %	Risk of High Toxicity
Scenario 5	Pr(Toxicity)	.07	.15	.25	.38	.52		
Uniform	BOIN	2.6	33.4	**45.3**	16.6	2.1	57.8	6.3
	# patients	6.9	10.2	**8.5**	3.7	0.7		
	TITE-BOIN	22.2	**27.8**	14.1	3.0	0.4	70.6	12.8
	# patients	4.7	**8.7**	11.9	7.9	2.8		
Weibull	BOIN	0.0	1.2	**90.4**	8.4	0.0	34.6	0.4
	# patients	3.2	5.8	**19.8**	6.9	0.3		
	TITE-BOIN	4.1	**24.3**	0.0	0.0	0.0	46.1	54.9
	# patients	3.0	**4.7**	20.3	7.9	0.0		

Appendix A

Appendix

A.1 Clinical Trial Overview

In addition to Phase I of a clinical trials, there a other a new cancer drug must pass when seeking to be admitted into the market. A brief description of what takes place in each of the trials is as follows:

- Phase I: Research is done on a new drug or treatment on a small group of people for the first time to evaluate the safety, determine a safe dosage range, and identify side effects.

- Phase II: The drug or treatment is given to a larger group of people to determine if it remains effective and to further evaluate its safety.

- Phase III: The drug or treatment effectiveness is confirmed by giving it to a large group of people, monitoring side effects, comparing it to commonly used treatments, and collecting information that will allow the drug or treatment to be used safely.

- Phase IV: After the drug or treatment has been marketed, studies are done to gather information on the drug's effect in various populations and any side effects with long-term use.

Bibliography

[1] Y. G. Liu, S. and Y. Yuan, "Bayesian data augmentation dose finding with continual reassessment method and delayed toxicity," *The Annals of Applied Statistics*, 2013.

[2] Storer, "Design and analysis of phase i clinical trials," *Biometrics*, 1989.

[3] M. D. C. T. R. L. C. M. Korn, E.L. and R. Simon, "A comparison of two phase i trial designs," *Stat. Med.*, 1994.

[4] P. M. O'Quigley, J. and L. Fisher, ""continual reassessment method: A practical design for phase i clinical trials in cancer"," *Biometrics*, 1990.

[5] L. J. Torneau, C. and L. Siu, "Dose escalation methods in phase i cancer clinical trials," *Journal of National Cancer Institue*, 2009.

[6] S. Liu and Y. Yuan, "Bayesian optimal interval design for phase i clinical trials.".

[7] A. D. Oron, A. and P. Hoff, ""dose-finding designs: The role of convergence properties"," *Int. J. Biostat.*, 2011.

[8] Y. Cheung and R. Chappell, "Sequential designs for phase i clinical trials with late onset toxicities," *Biometrics*, 2000.

[9] C. M. Wages, N. and J. O'Quigley, "Using the time-to-event continual reassessment method in the presence of partial orders," *Stat Med*, 2013.