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Dose-Finding when the Target Dose Is on a Plateau of a Dose-Response Curve: Comparison of Fully Sequential Designs

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Abstract

Consider the problem of estimating a dose with a certain response rate. Many multistage dose-finding designs for this problem were originally developed for oncology studies where the mean dose-response is strictly increasing in dose. In non-oncology Phase II dose-finding studies the dose-response curve often plateaus in the range of interest and there are several doses with the mean response equal to the target. In this case it is usually of interest to find the lowest of these doses since higher doses might have higher adverse event rates. It is often desirable to compare the response rate at the estimated target dose with a placebo and/or active control. We investigate which of the several known dose-finding methods developed for oncology Phase I trials is the most suitable when the dose response curve plateaus. Some of the designs tend to spread the allocation among the doses on the plateau. Others, like the continual reassessment method and the *t*-statistic design, concentrate allocation at one of the doses with the *t*-statistic design selecting the lowest dose on the plateau more frequently.

Keywords

Proof-of-concept; Phase II trials; Group up-and-down designs; Continual reassessment method; *t*-statistic design

1. INTRODUCTION

Estimating the doses of interest with high precision in non-oncology Phase II studies is vital for the future development of a drug. The goal of a Phase II study is often to find the lowest dose with a certain expected target response rate. Often it is also of interest to compare the response or adverse event rates at the target dose to placebo or active control. Hall, Meier, and Diener [1] described a proof-of-concept trial for the treatment of migraine headaches. There were two goals in the study. The first goal was to find the lowest dose with the response rate of 0.6, and the second goal was to compare the response rate at the estimated dose with placebo. Two of the seven scenarios considered by Hall et al. [1], (0.3,0.3,0.4,0.5,0.6,0.6,0.6) and (0.3,0.6,0.6,0.6,0.6,0.6,0.6), had several doses with the target response rate of 0.6. It is not unlikely in a Phase II trial that the response rates will plateau around the rate of interest. When there are several doses with the mean response equal to the target, the investigators are interested in finding the lowest of these doses. One of the reasons is because such a dose is likely to have a more favorable adverse event

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profile. To achieve the second goal of comparison to a placebo it is important to maximize the number of patients at the estimated target dose.

If response can be observed relatively quickly compared to the accrual rate, adaptive designs might be an attractive alternative to a single-stage design because they yield improved quality of information for the same total sample size. By improved quality of information we mean not only the higher power of comparison to placebo but also, for example, the ability to study more doses. Both fully sequential designs [2,3,4,5,6] where adaptations are performed after each cohort of patients and two-stage designs [7,8,9,10] can be considered. Here we focus on fully sequential designs as these generally yield higher expected sample size at the estimated target dose and therefore yield a higher power of comparison to placebo than single and two-stage designs. When considering what design to choose for a trial, we recommend investigating all design options including a single stage, two-stage and fully sequential designs, while taking into consideration the trade-off between improved quality of information and more complex logistics of the trial as the number of stages increases. Time to observe the outcome compared to the rate of accrual should also be taken into account as well. Most fully sequential dose-finding designs, except for the Normal Dynamic Linear Model (NDLM) [6], have been developed for dose-finding in oncology where dose has to be escalated gradually and an increasing dose-response relationship is assumed. The NDLM method [6], on the other hand, does not make any monotonicity assumptions on the dose-response curve. The NDLM has been compared with *t*-statistics type designs to estimate ED90 when the dose-response curve plateaus [11]. The NDLM tended to spread allocation across the dose range and was inferior to the *t*-statistic designs as far as estimation of ED90 and the number of patients assigned to the estimated ED90. For strictly increasing curves the CRM was compared with the *t*-statistic design in [5]. The CRM performs better for smaller sample sizes (25 patients in a six-dose study) and both designs perform similarly for larger sample sizes (48 patients in a six-dose study). In this paper we investigate the performance of several fully sequential dose-finding designs where the dose-response curve plateaus in the range of interest. The designs studied are group designs [2,3], the continual reassessment method (CRM) [4], and the dose-finding design based on *t*-statistic [5]. We study design performance via simulations. Additionally performance of group designs is studied theoretically.

2. GROUP DESIGNS

Let $D = \{d_1,..,d_K\}$ be the ordered set of doses selected for the study. A patient's response at d_k is a Bernoulli random variable with parameter p_k, where $p_1 \leq .. \leq p_K$. The goal is to find the lowest dose with the response rate Because we are interested in the situation where there is a plateau at the target response rate, we will consider scenarios where $p_1 < p_2 < \ldots < p_j = \ldots = p_K =$ Note that if the plateau is considerably below or above the target, the designs will perform as well as they perform for a strictly increasing curve because in that case there is only one dose with the mean response closest to the target.

First we consider a group design, as this was selected by the investigators of the migraine headache trial [1]. Patients are treated in cohorts of size s starting with the lowest dose. Let $X(d_j) \sim \text{Bin}(s, p_j)$ be the number of patients with response in the most recent cohort assigned to dose d_j. Let c_L and c_U be two integers such that $0 \leq c_L < c_U \leq s$. Assume that the most recent cohort of patients was assigned to dose level d_j, $j = 1,\ldots, K$. Then

1. If $X(d_j) \leq c_L$, the next cohort of s patients is assigned to dose d_{j+1};
2. If $c_L < X(d_j) < c_U$, the dose is repeated for the next cohort of s patients;
3. If $X(d_j) \geq c_U$, the next cohort of s patients is assigned to dose d_{j-1}.

Appropriate adjustments are made at the lowest and highest doses. The process is continued until the total sample size specified in advance is reached. This design is denoted as $UD(s, c_L, c_U)$, where s is the cohort size, c_L is the lower cut-off and c_U is the upper cut-off.

Hall et al. [1] used $UD(4,2,3)$ in the headache trial, where the dose is increased if 2 or less responses were observed, and the dose is reduced if 3 or more responses were observed. When the dose-response curve is strictly increasing, $p_1 < \ldots < p_K$, the assignments in a group design will cluster around the dose with response rate Γ^* [12], where Γ^* is the solution of

$$\Pr\{\mathrm{Bin}(s, \Gamma^*) \le c_L\} = \Pr\{\mathrm{Bin}(s, \Gamma^*) \ge c_U\}. \quad (1)$$

For $UD(4,2,3)$, $\Gamma^* = 0.6143$. Therefore, it was appropriate to use $UD(4,2,3)$ to target the response rate of $\Gamma = 0.6$. See Ivanova et al. [12] for guidelines on how to choose design parameters s, c_L, c_U to target desired quantile Γ. The investigators of the trial justified using $UD(4,2,3)$ for $\Gamma = 0.6$ via simulations. The question is how well this group design behaves if the condition $p_1 < \ldots < p_K$ is violated. The theorem below states that for a dose-response curve with $p_1 < p_2 < \ldots < p_j = \ldots = p_K = \Gamma^*$, for large total sample sizes the assignments will be equally spread over doses $d_j, \ldots, d_K$ rather than concentrating on one of these doses.

THEOREM

If the true response rates are $p_1 < p_2 < \ldots < p_j = \ldots = p_K = \Gamma^*$ and the solution of equation (1) for a group design $UD(s, c_L, c_U)$ is equal to Γ^*, the mode of the stationary distribution for the assignments of $UD(s, c_L, c_U)$ spans doses $d_j, \ldots, d_K$. The proof of the theorem is in the Appendix.

For example, if response rates at the doses are (0.3, Γ^*, Γ^*, Γ^*, Γ^*, Γ^*, Γ^*,) with $\Gamma^* = 0.6143$, and the total sample size in the trial is relatively large, the proportions of patients allocated to the seven doses by $UD(4,2,3)$ in the limit is (π_1, $\pi\pi\pi\pi\pi\pi$) with $\pi_1 = 0.082$ and $\pi = 0.153$. The more doses that are on the plateau, the smaller the proportion of patients allocated to each of the doses on the plateau and the smaller the power of comparison with placebo.

3. DOSE FINDING BASED ON *t*-STATISTIC

The t-statistic design was proposed by Ivanova and Kim [5]. It can be used with binary as well as continuous outcome. Let $\mathbf{n}(t) = (n_1(t), \ldots, n_K(t))$ be the number of patients at each of the K doses right after patient t, $t \le N$, has been assigned, that is, $n_1(t) + \ldots + n_K(t) = t$. Let Y_{ji} be the observation from the ith patient assigned to dose d_j, $i = 1, .., n_j(t)$. Let $\widehat{p}_j = \sum_{i=1}^{n_j(t)} Y_{ji} / n_j(t)$ be the current estimate of response rate at dose d_j, computed from all patients assigned to d_j so far. Define $T_j(n_j(t))$, $n_j(t) \ge 2$, to be the t-statistic

$$T_j\left(n_j(t)\right) = \frac{\widehat{p}_j - \Gamma}{\sqrt{\widehat{p}_j\left(1 - \widehat{p}_j\right)} / \sqrt{n_j(t)}}.$$

If $\widehat{p}_j = 0$ or 1, $T_j(n_j(t))$ is equal to $+\infty$ or $-\infty$ depending on the sign of $\widehat{p}_j - \Gamma$. Patients are assigned in cohorts. Suppose the most recent patient t was assigned to dose d_j. The next cohort of patient is assigned as follows:

i. if $T_j(n_j(t)) \le -\lambda$, the next patient is assigned to dose d_{j+1};

ii. if $T_j(n_j(t)) \geq \lambda$, the next patient is assigned to dose d_{j-1};

iii. if $-\varepsilon < T_j(n_j(t)) < \lambda$, the next patient is assigned to dose d_j.

Ivanova and Kim [5] recommended to set design parameter $\varepsilon = 1$. The performance of the *t*-statistic design where there is a plateau in the range of interest is assessed by simulations in Section 5.

4. CONTINUAL REASSESSMENT METHOD (CRM)

The CRM is a dose-finding method proposed by O'Quigley et al. [4]. It uses a working model for dose-response relationship, for example, where $p_i = b_i^{\theta}$, where $(b_1,\ldots,b_K)$ is a set of constants and θ is a parameter to be estimated. The CRM has been shown to converge to the target dose if used in continuous dose space [13]. If used with discrete doses, given a working model, the CRM converges to the dose with the true response rate closest to the target or to doses with response rates within a so called indifference interval from the target [14]. The argument from [14] could be extended to the case where a dose-response curve plateaus in the region of interest to show that the CRM converges to one of the doses on a plateau or a dose within indifference interval. The CRM yields an increased sample size at one of the doses on the plateau or a nearby dose with response close to λ, although this dose might not be the lowest dose on the plateau. In the simulation study we used the model from [4] with $(b_1,\ldots,b_7) = (0.1,0.2,0.3,0.4,0.5,0.6,0.7)$ and exponential prior with mean 1 for parameter θ. In simulations with 3 and 4 doses (b_1,b_2,b_3) and (b_1,b_2,b_3,b_4) were used correspondingly. A number of modifications of the CRM have been proposed [15,16]. In the simulations study we used the modification where skipping untried doses is not allowed if the dose is escalated.

5. SIMULATION STUDY

In addition to the two scenarios from Hall et al. [1], one more scenario with 7 doses of the drug, two scenarios with 4 doses and two scenarios with 3 doses were used to compare the different designs in our simulation study. Table I displays mean efficacy rates and mean adverse event rates for the drug. Placebo efficacy rate is 0.3 and placebo adverse event rate is 0.1. The target treatment response rate is $\lambda = 0.6$. Results for each design/scenario combination are based on 5000 simulation runs. We investigated the performance of the group design *UD*(4,2,3) used in Hall et al. [1], the CRM, the *t*-statistic design[5] and a single-stage design with equal allocation to all doses. The maximum total sample size was fixed at 120 patients with 40 patients assigned to a placebo and 80 to various doses of the drug. This sample size was chosen because 40 patients per group yields 80% power if treatments with true rates of 0.3 and 0.6 are compared using a one-sided 0.05 level test. Patients were assigned in cohorts of 6 with 2 patients assigned to placebo and 4 to a dose of the drug. At the end of the trial, response rates for all designs except the CRM were estimated using isotonic regression [17] and then the dose with the estimated response rate closest to the target was declared the estimated target dose. If there were two or more such doses, the highest dose with the estimated value below λ was chosen. If all the estimated values at these doses were higher than λ, the lowest of these doses was chosen. For the CRM, the estimated target dose was defined as the dose that would have been recommended for the next patient [4].

The ability to stop for futility is one of the most important features of an adaptive dose-finding trial. One interim analysis was performed as soon as 28 patients were assigned to the highest dose, at which point the response rate at the highest dose was compared to the response rate of placebo. The trial was stopped for futility if the one-sided p-value based on Fisher's exact test was higher than 0.2. The futility rule was chosen in such a way that the

probability of stopping the trial with at least one good dose for the *t*-statistic design is at most 0.01. If the trial was stopped for futility at the interim analysis, no dose was selected as the estimated target dose.

The primary goal of our study was to estimate the target dose. Table II shows the selection probability of each dose as the estimated target dose under each design. All designs performed well in selecting a dose with the target response rate, not necessarily the lowest, with the CRM performing the best in scenarios 2 and 3 where at least a part of the dose-response curve is gradually increasing. The results for the lowest dose on the plateau are in bold. The *t*-statistic design selects the lowest dose on the plateau more frequently than others in 5 out of 7 scenarios. The last column of Table II shows proportion of trials that were stopped earlier for futility. About 30% of the trails were stopping early for futility in scenario 4 and 75% in the null scenario 5 (scenarios not shown in Table 2).

The average sample size at each dose is shown in Table III, with the results for the lowest dose on the plateau shown in bold. The planned total number of patients in the trial including placebo was 120. Addition of early futility stopping yielded 112 total patients on average in scenario 4 and 98 patients on average in the null scenario 5. We choose to use a conservative stopping rule that yields the probability of less than 0.01 of stopping a trial if there is at least one dose with efficacy rate higher than the placebo rate by at least 0.3. If a less conservative rule is chosen, a trial with ineffective drug will stopped with higher probability resulting in lower average total sample size.

One of the goals of the trial was to compare the response rate at the estimated target dose with placebo. That is why our goal was to maximize the sample size at the estimated target dose. The distribution of the sample size at the estimated target dose is displayed in Table IV. The CRM and the *t*-statistic design have larger average sample size at the estimated target dose compared to the group design and equal allocation. The larger sample size translates into a higher power when the estimated target dose is compared to placebo with respect to efficacy (results are available from the authors). The CRM and the *t*-statistic design yield a very similar power of this comparison. The group design yields power 0.1 to 0.2 less than the other two designs with even less power for equal allocation. Efficacy was compared using one-sided 0.05 level Fisher's exact test.

The lowest dose on the plateau is often of interest because it is likely to have a better adverse event profile than higher doses. We constructed plausible adverse event rate scenarios (Table I), and compared the estimated dose with placebo based on both efficacy and adverse event rates. The adverse event rate at the estimated dose was compared with the rate of placebo using one-sided 0.05 level test with the null hypothesis that the adverse event rate of the drug is higher than placebo rate plus 0.2. Table V displays the proportion of trials where the estimated target dose is shown to have an efficacy rate significantly better than the placebo rate and an adverse event rate significantly lower than the placebo rate plus 0.2. As far as power for joint comparison, the *t*-statistic design is significantly better than the CRM in scenarios 1, 6, 7, and 8 and the CRM performs slightly better or similarly in scenarios 2, 3, and 9, where at least one part of the curve has a gradual increase. This is because both designs yield a large sample size at the estimated target dose, on average, with the *t*-statistic design selecting the lowest dose on the plateau more often than the CRM. The power for the group design and equal allocation is not as good as for the CRM or the *t*-statistic designs.

6. CONCLUSION

It is not uncommon in a Phase II non-oncology study for a dose-response curve to plateau, yielding several doses with the same mean response. We investigated the performance of

several oncology Phase I dose-finding designs developed for strictly increasing curves in the case where a dose-response curve plateaus in the range of interest. We have demonstrated theoretically and by simulations that a group design is not a good choice when a dose-response curve plateaus near the response rate of interest. Based on our simulations study we conclude that the *t*-statistic design performs better than the group design and the CRM as it assigns many patients to the estimated target dose and selects the lowest dose on the plateau more often than the other two designs.

We considered the case where a dose-response curve is assumed to be non-decreasing. The methods we have studied are not appropriate when there might be a down-turn in a dose-response curve at higher doses or the goal is to find the maximum of a utility function that quantifies efficacy-tolerability trade-offs. Methods such as [6,10,18] can be used with such umbrella shaped curves.

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APPENDIX A

Proof of Theorem

Let α_j, β_j, γ_j denote the probabilities to decrease the dose from d_j to d_{j-1} to repeat the dose d_j, or increase the dose from d_j to d_{j+1} in $UD(s,c_L,c_U)$. Here $\alpha_j + \beta_j + \gamma_j = 1$ for $j \in \{1,\ldots,K\}$ are the elements of jth row of transition matrix P, with β_j being a diagonal element, and α_j and γ_j being to the left and to the right of β_j. These probabilities can be computed as follows

$$\begin{gathered}\alpha_1=0,\beta_1=1-\gamma_1,\gamma_1=\Pr\{Bin(s,p_1)\le c_L\},\\ \alpha_j=\Pr\left\{Bin\left(s,p_j\right)\ge c_U\right\},\beta_j=\Pr\left\{c_L<Bin\left(s,p_j\right)<c_U\right\},\gamma_j=\Pr\left\{Bin\left(s,p_j\right)\le c_L\right\},\\ \alpha_K=\Pr\{Bin(s,p_K)\ge c_U\},\beta_K=1-\alpha_K,\gamma_K=0,\end{gathered}$$

where $j \in \{2,\ldots,K-1\}$. The stationary distribution $\pi = (\pi_1,\ldots,\pi_K)$ can be obtained by solving the balance equations , $\pi_j = \pi_{j-1}\gamma_{j-1} + \pi_j\beta_j + \pi_{j+1}\alpha_{j+1}$, $j \in \{1,\ldots,K\}$ (here for convenience $\alpha_0 = \gamma_{K+1} = 0$). The solution is

$$\pi_j=\prod_{i=1}^{j}\lambda_i,\quad \lambda_1=\left(1+\sum_{j=2}^{K}\prod_{i=2}^{j}\lambda_i\right)^{-1},\quad \lambda_i=\frac{\gamma_{i-1}}{\alpha_i},$$

where $j \in \{2,\ldots,K\}$. Gezmu and Flournoy (2006) showed that γ_j decreases with j while α_j increases with j, so similarly to Durham and Flournoy (1994), the stationary distribution is log-concave, also the mode spans d_{k-1} and d_k if $\beta_k = 1$. Since $p_1 < p_2 < \ldots < p_j = \ldots = p_K = \theta^*$ and θ^* is a solution of equation (1), $\beta = \beta_i = \beta$ for all $i = j,\ldots,K$. Hence $\pi_j = \pi_{j-1} / \alpha_i = \pi \beta = 1$ for $i = j+1,\ldots,K$, and the mode spans doses $d_{(j+1)-1},\ldots, d_K$.

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Table I

Mean efficacy scenarios with corresponding adverse event rates (drug only). Placebo efficacy is 0.30 and the rate of adverse events on placebo is 0.1. Adverse event scenarios are used to illustrate which design selects the lowest dose on plateau.

Scenario	Mean response curve	Adverse event rate
1	(0.30,0.60,0.60,0.60,0.60,0.60,0.60)	(0.1,0.1,0.2,0.3,0.4,0.5,0.6)
2	(0.30,0.30,0.40,0.50,0.60,0.60,0.60)	(0.1,0.1,0.1,0.1,0.1,0.2,0.3)
3	(0.30,0.40,0.50,0.60,0.70,0.80,0.90)	(0.1,0.1,0.1,0.1,0.2,0.3,0.4)
4	(0.30,0.30,0.33,0.36,0.39,0.42,0.45)	(0.1,0.1,0.1,0.1,0.1,0.1,0.1)
5	(0.30,0.60,0.60,0.60,0.60,0.60,0.60)	(0.1,0.1,0.1,0.1,0.1,0.1,0.1)
6	(0.50,0.60,0.60,0.60)	(0.1,0.1,0.2,0.3)
7	(0.40,0.50,0.60,0.60)	(0.1,0.1,0.1,0.2)
8	(0.50,0.60,0.60)	(0.1,0.1,0.2)
9	(0.50,0.60,0.70)	(0.1,0.1,0.3)

Table II

Proportion of trials in which a dose was selected as the estimated target dose and proportion of trials stopped earlier for futility. Only scenarios with at least one active dose are included.

Scenario	d_1	d_2	d_3	d_4	d_5	d_6	d_7	*Futility*
Scenario 1								
Group design	0.00	**0.32**	0.15	0.13	0.11	0.12	0.15	0.01
CRM	0.01	**0.27**	0.25	0.23	0.16	0.07	0.01	0.00
t-statistic design	0.00	**0.66**	0.20	0.09	0.03	0.01	0.01	0.00
Equal allocation	0.01	**0.30**	0.14	0.11	0.11	0.12	0.21	-
Scenario 2								
Group design	0.00	0.00	0.01	0.18	**0.30**	0.21	0.27	0.02
CRM	0.00	0.00	0.00	0.19	**0.48**	0.26	0.06	0.01
t-statistic design	0.00	0.00	0.02	0.30	**0.45**	0.16	0.07	0.00
Equal allocation	0.00	0.00	0.03	0.16	**0.30**	0.21	0.30	-
Scenario 3								
Group design	0.00	0.01	0.24	**0.55**	0.19	0.01	0.00	0.00
CRM	0.00	0.00	0.16	**0.63**	0.20	0.00	0.00	0.00
t-statistic design	0.00	0.01	0.27	**0.57**	0.14	0.00	0.00	0.00
Equal allocation	0.00	0.04	0.28	**0.51**	0.17	0.01	0.00	-
Scenario 6								
Group design	0.13	**0.32**	0.21	0.28				0.06
CRM	0.11	**0.37**	0.24	0.23				0.06
t-statistic design	0.22	**0.49**	0.18	0.10				0.01
Equal allocation	0.13	**0.30**	0.22	0.35				-
Scenario 7								
Group design	0.01	0.19	**0.40**	0.35				0.00
CRM	0.00	0.14	**0.39**	0.38				0.00
t-statistic design	0.01	0.25	**0.48**	0.22				0.00
Equal allocation	0.01	0.15	**0.40**	0.44				-
Scenario 8								
Group design	0.15	**0.41**	0.34					0.00
CRM	0.12	**0.37**	0.40					0.00
t-statistic design	0.21	**0.50**	0.25					0.00
Equal allocation	0.16	**0.41**	0.43					-
Scenario 9								
Group design	0.19	**0.64**	0.16					0.00
CRM	0.15	**0.63**	0.19					0.00
t-statistic design	0.21	**0.65**	0.14					0.00
Equal allocation	0.23	**0.62**	0.16					-

Table III

Average number of patients at each dose of the drug. Only scenarios with at least one active dose are included.

Scenario	d_1	d_2	d_3	d_4	d_5	d_6	d_7
Scenario 1							
Group Design	14	**19**	15	11	8	7	6
CRM	7	**22**	20	17	11	3	0
t-statistic design	14	**45**	13	5	1	0	0
Equal allocation	15	**15**	15	15	15	15	15
Scenario 2							
Group Design	5	6	11	**16**	16	13	12
CRM	4	4	6	**18**	28	15	3
t-statistic design	7	7	12	**25**	21	6	2
Scenario 3							
Group Design	7	12	19	**22**	14	6	1
CRM	5	6	16	**34**	17	2	0
t-statistic design	7	13	27	**26**	7	1	0
Scenario 6							
Group Design	20	**22**	19	19			
CRM	17	**26**	18	17			
t-statistic design	33	**32**	10	4			
Equal allocation	24	**24**	24	24			
Scenario 7							
Group Design	12	20	**23**	23			
CRM	7	16	**26**	28			
t-statistic design	13	28	**27**	11			
Scenario 8							
Group Design	23	**27**	27				
CRM	17	**26**	26				
t-statistic design	32	**32**	14				
Equal allocation	30	**30**	30				
Scenario 9							
Group Design	26	**31**	23				
CRM	19	**37**	22				
t-statistic design	32	**37**	10				

Table IV

The distribution of the number of patients assigned to the estimated target. Only scenarios with at least one active dose are included.

	Min	1st	Median	3th	Max
Scenario 1					
Group Design	4	16	24	28	44
CRM	4	36	52	60	76
t-statistic design	4	40	56	68	76
Scenario 2					
Group Design	4	16	20	28	52
CRM	4	32	48	56	68
t-statistic design	4	24	36	48	72
Scenario 3					
Group Design	4	20	24	28	40
CRM	4	32	44	56	72
t-statistic design	4	28	40	52	76
Scenario 6					
Group Design	4	24	28	32	64
CRM	4	40	56	64	80
t-statistic design	4	36	52	68	80
Scenario 7					
Group Design	4	24	28	32	64
CRM	4	40	56	68	80
t-statistic design	4	32	44	60	80
Scenario 8					
Group Design	12	28	32	36	60
CRM	4	44	60	72	80
t-statistic design	4	40	52	68	80
Scenario 9					
Group Design	8	32	32	36	60
CRM	4	36	52	64	80
t-statistic design	4	36	52	68	80

Table V

Proportion of trials where the estimated target dose is showr to have an efficacy rate significantly better than placebo rate and adverse event rate significantly lower than placebo rate plus 0.2.

Scenario	Group design	CRM	*t*-statistic design	Equal allocation
Scenario 1	0.29	0.30	0.61	0.09
Scenario 2	0.37	0.53	0.55	0.10
Scenario 3	0.54	0.61	0.60	0.12
Scenario 4	0.27	0.25	0.25	0.05
Scenario 5	0.03	0.03	0.03	0.01
Scenario 6	0.39	0.44	0.57	0.25
Scenario 7	0.50	0.50	0.58	0.30
Scenario 8	0.51	0.49	0.60	0.40
Scenario 9	0.58	0.57	0.61	0.45