Escalation with Overdose Control using Ordinal Toxicity Grades for Cancer Phase I Clinical Trials

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Summary

Dose finding studies in early phase cancer clinical trials are sequential designs aimed at estimating a maximum tolerated dose (MTD) for further phase II studies of efficacy. The majority of the statistical designs that were proposed in the last two decades allocate future doses based on a binary outcome of dose limiting toxicity (DLT) of previously treated patients. Such designs may not be efficient in the sense that the dose recommended for the next patient is the same regardless whether the previously treated patient had no toxicity or had intermediate grade 2 toxicity. In this article, we extend a Bayesian adaptive phase I clinical trial design known as escalation with overdose control (EWOC) by introducing an intermediate grade 2 toxicity when assessing DLT. Under the proportional odds model assumption of dose-toxicity relationship, we prove that in the absence of DLT, the dose allocated to the next patient given that the previously treated patient had a maximum of grade 2 toxicity is lower than the dose given to the next patient had the previously treated patient exhibited a grade 0 or 1 toxicity at the most. Further, we prove that the coherence properties of EWOC are preserved. Simulation results show that the safety of the trial is not compromised and the efficiency of the estimate of the MTD is maintained relative to EWOC treating DLT as a binary outcome and that fewer patients are overdosed using this design when the true MTD is close to the minimum dose.

Key Words: EWOC; Cancer phase I trials; MTD; Ordinal toxicity grades; Coherence; Proportional odds model.

1. Introduction

Cancer phase I clinical trials are sequential designs enrolling late stage cancer patients who have exhausted standard treatment therapies [1]. For cytotoxic agents or combinations of biologic with cytotoxic drugs, the main objectives of these trials are to characterize treatment related toxicities and estimate a dose level that is associated with a pre-determined level of dose limiting toxicity (DLT). Such a dose is called maximum tolerated dose (MTD) or phase II dose. Specifically, the MTD, γ, is defined as the dose that is expected to produce DLT after one cycle of therapy in a specified proportion θ of patients:

$$P(DLT \mid Dose = \gamma) = \theta. \qquad (1.1)$$

Model based designs for cancer phase I clinical trials have been studied extensively in the last two decades, see O'Quigley et al. [2], Gatsonis and Greenhouse [3], Durham and Flournoy [4], Korn et al. [5], Whitehead and Brunier [6], Whitehead [7], Babb et al. [8], Gasparini and Eisele [9], Mukhopadhyay [10], and Haines et al. [11]. Escalation with overdose control (EWOC) originally proposed by Babb et al. [8] is another alternative Bayesian outcome adaptive design for dose finding in early phase cancer trials. Its

main feature is that at each stage of the trial, we seek a dose for which the posterior probability of exceeding the MTD γ is bounded by a feasibility bound α.

The above methods allocate future doses based on a binary outcome of DLT of previously treated patients The work we present in this manuscript is motivated by the ethical concern raised by clinical colleagues regarding dose escalation in the absence of DLT. Specifically, if the current patient experiences drug related grade 2 toxicity at the most, then the dose to be allocated to the next patient should not be as high as the one had the current patient experienced a maximum of grade 0 or 1 toxicity. We present a Bayesian outcome adaptive design which is an extension of EWOC by accommodating an intermediate grade 2 toxicity to the model. We use a proportional odds model to describe the dose-toxicities relationship and the design is termed EWOC proportional odds model, written as EWOC-POM. We show that the design satisfies the above ethical consideration without compromising the safety and efficiency of the trial. Furthermore, we show that the design maintains the coherence properties of EWOC.

2. Method

2.1. *Model*

Let $G = 0,1,\ldots,4$ be the maximum grade of toxicity experienced by a patient by the end of one cycle of therapy and define DLT as a maximum of grade 3 or 4 toxicity. Let

$$Y = \begin{cases} 0 \text{ if } G = 0 \text{ or } 1 \\ 1 \text{ if } G = 2 \\ 2 \text{ if } G = 3 \text{ or } 4 \end{cases} \tag{2.1}$$

We model the dose-toxicities relationship by assuming that

$$P(Y \geq j \mid x) = F(\alpha_j + \beta x),\ j = 1,2, \tag{2.2}$$

where $F(\cdot)$ is a known strictly increasing c.d.f. This implies that $\alpha_2 \leq \alpha_1$. We assume that $\beta > 0$ so that the probability of DLT is an increasing function of dose. The MTD, γ, is defined as the dose that is expected to produce DLT in a specified proportion θ of patients:

$$P(Y = 2 \mid x = \gamma) = F(\alpha_2 + \beta\gamma) = \theta. \tag{2.3}$$

Suppose that dose levels in the trial are selected in the interval $[X_{\min}, X_{\max}]$.

2.1.1. *Likelihood*

Let $D_n = \{(x_i, Y_i),\ i = 1,\ldots,n\}$ be the data after enrolling n patients to the trial. The likelihood function for the parameters α_1, α_2, and β is

$$\begin{aligned} &L(\alpha_1, \alpha_2, \beta \mid D_n) \\ &= \prod_{i=1}^{n} \left[1 - F(\alpha_1 + \beta x_i)\right]^{I(Y_i=0)} \left[F(\alpha_1 + \beta x_i) - F(\alpha_2 + \beta x_i)\right]^{I(Y_i=1)} \left[F(\alpha_2 + \beta x_i)\right]^{I(Y_i=2)}, \end{aligned} \tag{2.4}$$

where $I(\cdot)$ is the indicator function.

We reparameterize model (2.2) in terms of $\rho_0 = P(Y = 2 \mid x = X_{\min})$, the probability that a DLT manifests within the first cycle of therapy for a patient given dose $x = X_{\min}$, $\rho_1 = P(Y \geq 1 \mid x = X_{\min})$, the probability that a grade 2 or more toxicity manifests within the first cycle of therapy for a patient given dose $x = X_{\min}$, and the MTD γ. Assuming that the dose is standardized to be in the interval [0,1], it can be shown that

$$\begin{aligned} &\alpha_1 = F^{-1}(\rho_1),\ \alpha_2 = F^{-1}(\rho_0)\ , \\ &\beta = \frac{1}{\gamma}\left(F^{-1}(\theta) - F^{-1}(\rho_0)\right). \end{aligned} \tag{2.5}$$

The conditions $\alpha_2 \leq \alpha_1$, $\beta > 0$, and (2.2) imply that $0 \leq \rho_0 \leq \rho_1$ and $0 \leq \rho_0 \leq \theta$. Define

$$\begin{aligned} F_1(\rho_0, \rho_1, \gamma; x) &= F\left(F^{-1}(\rho_1) + \left(F^{-1}(\theta) - F^{-1}(\rho_0)\right)x / \gamma\right) \\ F_2(\rho_0, \rho_1, \gamma; x) &= F\left(F^{-1}(\rho_0) + \left(F^{-1}(\theta) - F^{-1}(\rho_0)\right)x / \gamma\right). \end{aligned} \tag{2.6}$$

Using (2.4), (2.5), and (2.6), the likelihood of the reparameterized model is

$$\begin{aligned} L(\rho_0, \rho_1, \gamma \mid D_n) = \prod_{i=1}^{n} &\left[1 - F_1(\rho_0, \rho_1, \gamma; x_i)\right]^{I(Y_i=0)} \left[F_1(\rho_0, \rho_1, \gamma; x_i) - F_2(\rho_0, \rho_1, \gamma; x_i)\right]^{I(Y_i=1)} \\ &\times \left[F_2(\rho_0, \rho_1, \gamma; x_i)\right]^{I(Y_i=2)}. \end{aligned} \tag{2.7}$$

2.1.2. *Prior and Posterior Distributions*

Let $g(\rho_0, \rho_1, \gamma)$ be the prior distribution on Ω, where $\Omega = \{(x,y,z): 0 \leq x \leq \theta,\ x \leq y \leq 1,\ X_{\min} \leq z \leq X_{\max}\}$. Using Bayes rule, the posterior distribution of the model parameters is proportional to the product of the likelihood and prior distribution

$$\pi(\rho_0, \rho_1, \gamma \mid D_n) \propto L(\rho_0, \rho_1, \gamma \mid D_n) \times g(\rho_0, \rho_1, \gamma). \tag{2.6}$$

We designed an MCMC sampler based on the Metropolis-Hastings algorithm ([12, 13] to obtain model operating characteristics. We also used WinBUGS [14] to estimate features of the posterior distribution of the MTD and design a trial. In the absence of prior information about the MTD and probability of DLT at $X_{\min}$, we specify vague priors for the model parameters as follows:

$$\begin{aligned} &\gamma \sim \text{Unif}[X_{\min}, X_{\max}] \\ &\rho_0 \sim \text{Unif}[0, \theta] \\ &\rho_1 \mid \rho_0 \sim \text{Unif}[\rho_0, 1]. \end{aligned} \tag{2.7}$$

2.1.3. *Trial Design*

Dose levels in the trial are selected in the interval $[X_{\min}, X_{\max}]$. The adaptive design proceeds as follows. The first patient receives a dose $x_1 > X_{\min}$ that is deemed to be safe by the clinician. Denote by $\Pi_k(\gamma) = \Pi(\gamma \mid D_k)$ the marginal posterior cdf of the MTD, $k = 1,\ldots,n\text{-}1$. The $(k+1)$-st patient receives the dose $x_{k+1} = \Pi_k^{-1}(\alpha)$ so that the posterior probability of exceeding the MTD is equal to the feasibility bound α. This is the overdose protection property of EWOC, where at each stage of the design, we seek a dose to allocate to the next patient while controlling the posterior probability of exposing patients to toxic dose levels. The trial proceeds until a pre-determined number of n patients are enrolled to the trial. At the end of the trial, we estimate the MTD as $\hat{\gamma} = \Pi_n^{-1}(\alpha)$.

3. Properties of EWOC-POM

3.1. *Characteristics of EWOC-POM*

The proposed design EWOC-POM assigns dose levels to future patients by taking into account the maximum observed toxicity grade during the first cycle of therapy according to the following properties.

(i) At each stage of the design, we seek a dose to allocate to the next patient while controlling the posterior probability of exposing patients to toxic dose levels.

(ii) If the maximum grade of toxicity experienced by patient k-1 within one cycle of therapy is grade 2, then the dose allocated to patient k is lower than the dose that would have been given to patient k had the maximum grade of toxicity experienced by patient k-1 been grade 0 or 1.

Characteristic (ii) is summarized in the following theorem.

THEOREM 1. Let $D_k = \{(Y_1, x_1),\ldots,(Y_k, x_k)\}$ be the data on the first k patients generated by the design described in Section 2.1.3 and $\Pi_k(\gamma;Y_k)$ be the cdf of γ given the data D_k. Let $x_{k+1} = \Pi_k^{-1}(\alpha;Y_k)$ and $x'_{k+1} = \Pi_k^{-1}(\alpha;Y'_k)$. Suppose that for all $x \in [X_{\min}, X_{\max}]$ and all (ρ_0,ρ_1) such that $0 \le \rho_0 \le \rho_1 \le 1$ and $\rho_0 \le \theta$, $(F_1 - F_2)/(1-F_1)$ is a monotonically decreasing function in γ. Then, $x'_{k+1} \ge x_{k+1}$ whenever $Y_k' = 0$ and $Y_k = 1$.

It is easy to verify that the monotonicity condition of Theorem 1 holds for the logistic function $F(w) = 1/(1+e^{-w})$. Using this link function and the uniform priors given in (2.7) with $\theta = 0.33$, Figure 1 gives all possible dose assignments for patients 1 and 2 and selected situations for patients 3 and 4 using the trial design described in Section 2.1.3. The dose has been standardized so that $X_{\min} = 0$ and $X_{\max} = 1$ and the first patient is given dose 0.10.

3.2. *Coherence of EWOC-POM*

In cancer phase I clinical trials, it is ethical not to increase a dose of a cytotoxic agent for the next patient if the previously treated patient exhibited DLT when given the same dose level. Furthermore, it is desirable not to decrease the dose of an agent for the next patient if the previously treated patient did not experience DLT when given that same dose level. These two properties are known as coherence is escalation and de-escalation, respectively, see Cheung [15]. A design that satisfies both of these properties is said to be coherent. Tighiouart and Rogatko [16] show that EWOC is coherent.

THEOREM 2. Suppose that for all x ϵ [X_{min}, X_{max}] and all (ρ_0,ρ_1) such that $0 \leq \rho_0 \leq \rho_1 \leq 1$ and $\rho_0 \leq \theta$, F_1 and F_2 are monotonically decreasing in γ. Then the design EWOC-POM described in 2.1.3 is coherent in de-escalation. Furthermore, if the toxicity response for patient k is $Y_k = 0$, then the dose allocated to patient k+1 satisfies $x_{k+1} \geq x_k$.

4. Simulation Studies

We compare the design operating characteristics of EWOC-POM with the original EWOC by simulating a large number of trials under several scenarios. We used the logistic function $F(w) = 1/(1+e^{-w})$ to model the dose-toxicities relationship in (2.2). EWOC was implemented as in Tighiouart et al. [17] using the same logistic function to model the dose-toxicity relationship. For all scenarios, we standardize the dose to be in the interval [0, 1], $\theta = 0.33$, the feasibility bound $\alpha = 0.25$, and the trial sample size is $n = 30$. The priors in (2.7) were adopted for EWOC-POM.

4.1. *Algorithm*

For a given scenario determined by ρ_0, ρ_1, and γ, the first patient receives dose 0 and the next dose x_2 is determined according to the trial design described in 2.1.3. The second response y_2 is then generated from model (2.2) reparametrized in terms of ρ_0, ρ_1, and γ with $x = x_2$. This process is repeated until all n patients have been enrolled to the trial. We considered 9 scenarios corresponding to a fixed value for $\rho_0 = 0.05$, three values of ρ_1, 0.2, 0.5, and 0.8, and three values of the MTD γ, 0.1, 0.5, and 0.7. For each model and each scenario, we simulated $M = 1000$ trials. EWOC and EWOC-POM were compared in terms of the proportion of patients exhibiting DLT, the average bias, $\text{bias}_{\text{ave}} = M^{-1}\left(\sum_{i=1}^{M}\hat{\gamma}_i - \gamma_{\text{true}}\right)$, and the estimated mean square error $\text{MSE} = M^{-1}\left(\sum_{i=1}^{M}(\hat{\gamma}_i - \gamma_{\text{true}})^2\right)$, where $\hat{\gamma}_i$ is the Bayes estimate of the posterior distribution of the MTD at the end of the i-th trial with respect to the asymmetric loss function

$$L(x,\gamma) = \begin{cases} \alpha(\gamma - x) & \text{if } x \leq \gamma \\ (1-\alpha)(x-\gamma) & \text{if } x > \gamma \end{cases}. \qquad (3.1)$$

We also compared the models with respect to the proportion of patients that were overdosed. Here, a dose x is defined as an overdose if $x > x^*$, where x^* is defined as the dose for which $P(\text{DLT} \mid x^*) = \theta + 0.05$. This probability is calculated using the parameter values from the corresponding scenario. These models are further compared with respect to the proportion of patients that were overdosed given that the previously treated patient exhibited grade 2 toxicity. Finally, we compared EWOC-POM to EWOC in terms of the proportion of trials for which the probability of DLT exceeds 0.4. This gives us an estimate of the probability that a prospective trial will result in an excessively high DLT rate. As for the proportion of trials with "correct MTD" recommendation, we presented percent of trials with estimated MTD within 5% and 10% of the dose range of the true MTD for EWOC-POM and EWOC.

4.2. *Results*

Figure 2 shows that the proportion of patients exhibiting DLT is always less than 34% for both EWOC and EWOC-POM under all scenarios and 4% fewer patients experiencing DLT under EWOC-POM when the MTD is small ($\gamma = 0.1$) and $\rho_1 = 0.8$. The same figure shows that the proportion of patients that are overdosed using EWOC is uniformly higher relative to EWOC-POM when the MTD is small. The same trend is observed when $\gamma = 0.5$ except when $\rho_1 = 0.2$. The difference in the proportion of patients being

overdosed when $\gamma = 0.7$ is negligible. The last panel of Figure 2 shows that the proportion of patients that are overdosed given that the previously treated patient exhibited grade 2 toxicity using EWOC is uniformly higher relative to EWOC-POM when $\gamma = 0.1, 0.5$ except when $\rho_1 = 0.2$. The difference in these proportions when $\gamma = 0.7$ is negligible. The last two columns of Table 1 show that the percent of trials with DLT rate of 0.4 or more is 7.5% at the most for EWOC and 6.6% for EWOC-POM. A more detailed comparison is shown in Figure 3, where side by side box plots of the distributions of the proportion of DLTs for EWOC-POM and EWOC under the nine scenarios are displayed. These results show that EWOC-POM maintains the safety of the trial relative to EWOC and is much safer when the true MTD is close to the minimum dose by reducing the number of patients that are exposed to toxic doses.

Figure 4 shows that the estimated MTDs using EWOC and EWOC-POM are very close in general, with the highest difference observed when $\rho_1 = 0.8$. This is reflected by the estimated bias and RMSE shown in Figure 4. This is expected since EWOC-POM is characterized by a conservative dose escalation when a patient experiences grade 2 toxicity. The highest absolute value of the bias is 0.04 and is achieved when $\gamma = 0.5, 0.7$ and $\rho_1 = 0.8$. This constitutes 4% of the range of the dose and is practically not significant. The percent of trials with estimated MTD within 5% of the dose range and 10% of the dose range of the true MTD γ under the nine scenarios are shown in columns 2-5 of Table 1. These results further confirm that the precision of the estimate of the MTD is similar between the two models, with a higher precision for EWOC achieved when $\gamma = 0.5$ and $\rho_1 = 0.8$. We conclude that EWOC-POM maintains the efficiency of the trial relative to EWOC for all practical purposes.

5. Discussion

In this article, we proposed a Bayesian adaptive design for dose finding studies in cancer phase I clinical trials. The method addresses the ethical concern regarding dose escalation in the absence of DLT. The method termed EWOC-POM is an extension of EWOC by accommodating an intermediate grade 2 toxicity to the model. We used a proportional odds model to describe the dose-toxicities relationship for simplicity. We proved that if the maximum grade of toxicity experienced by patient k–1 within one cycle of therapy is grade 2, then the dose allocated to patient k is lower than the dose that would have been given to patient k had the maximum grade of toxicity experienced by patient k–1 been grade 0 or 1. Furthermore, we also showed that the coherence properties of EWOC are maintained.

We studied design operating characteristics by simulating a large number of trials under different scenarios of the dose toxicity relationships. EWOC-POM was compared to EWOC with respect to the primary goals of cancer phase I trials; safety and efficiency of the estimate of the MTD. We found that in general, the safety of the trial is not compromised when we account for an intermediate grade 2 toxicity. In particular, when the unknown MTD is close to the initial dose, a substantial number of patients are overdosed when using EWOC relative to EWOC-POM and if the current patient experiences grade 2 toxicity, then the next patient is more likely to be overdosed using EWOC compared to EWOC-POM. The loss in efficiency of the estimate of the MTD by introducing an extra parameter to the model is very marginal as was shown by the simulation results of the various scenarios.

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6. References

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Appendix.

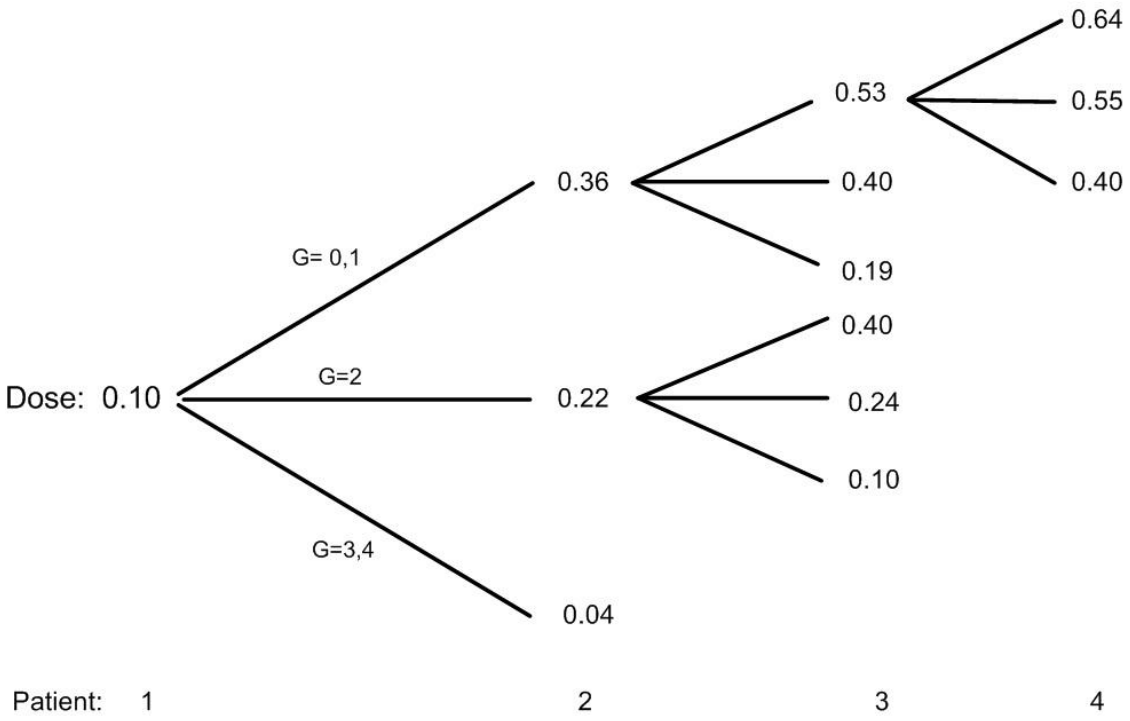

Figure 1. Tree of possible dose allocations for patients 1 and 2 and selected situations for patients 3 and 4. G=0,1 corresponds to Y = 0, G=2 corresponds to Y = 1, and G = 3,4 corresponds to Y = 2 or DLT.

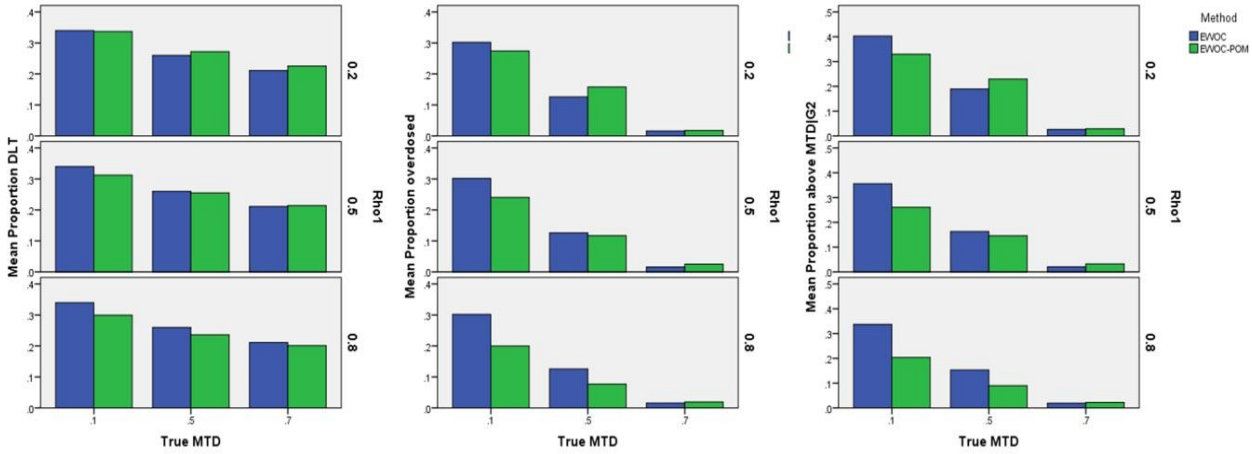

Figure 2. Summary statistics for trial safety for EWOC and EWOC-POM under all scenarios. Each graph represents mean proportion obtained from all patients from all 1000 simulated trials.

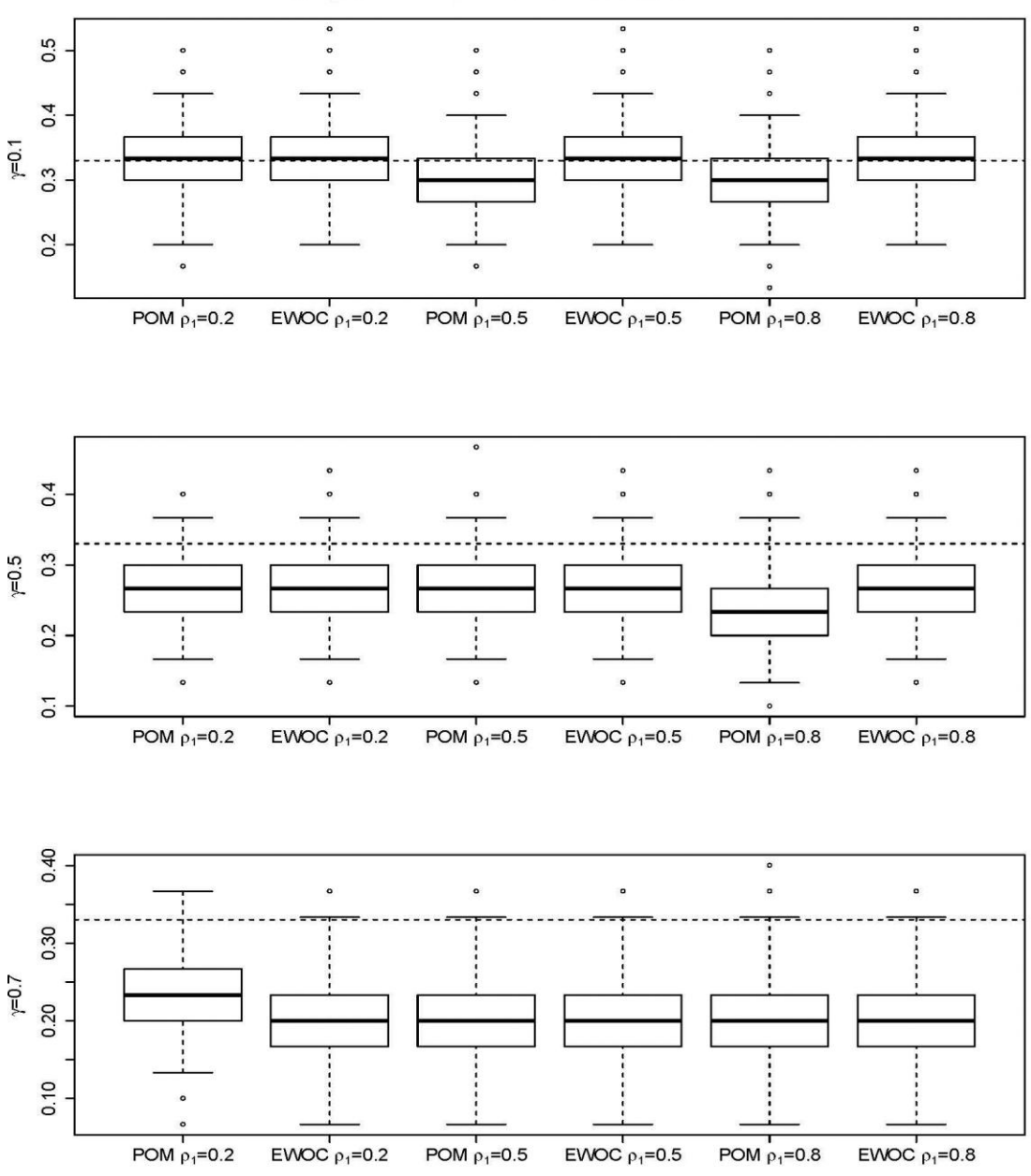

Figure 3. Box plots for the proportion of DLTs for EWOC-POM and EWOC under the nine scenarios. Each box plot was constructed from the DLT rates of the 1000 simulated trials. The dashed horizontal line corresponds to the target probability of DLT $\theta = 0.33$.

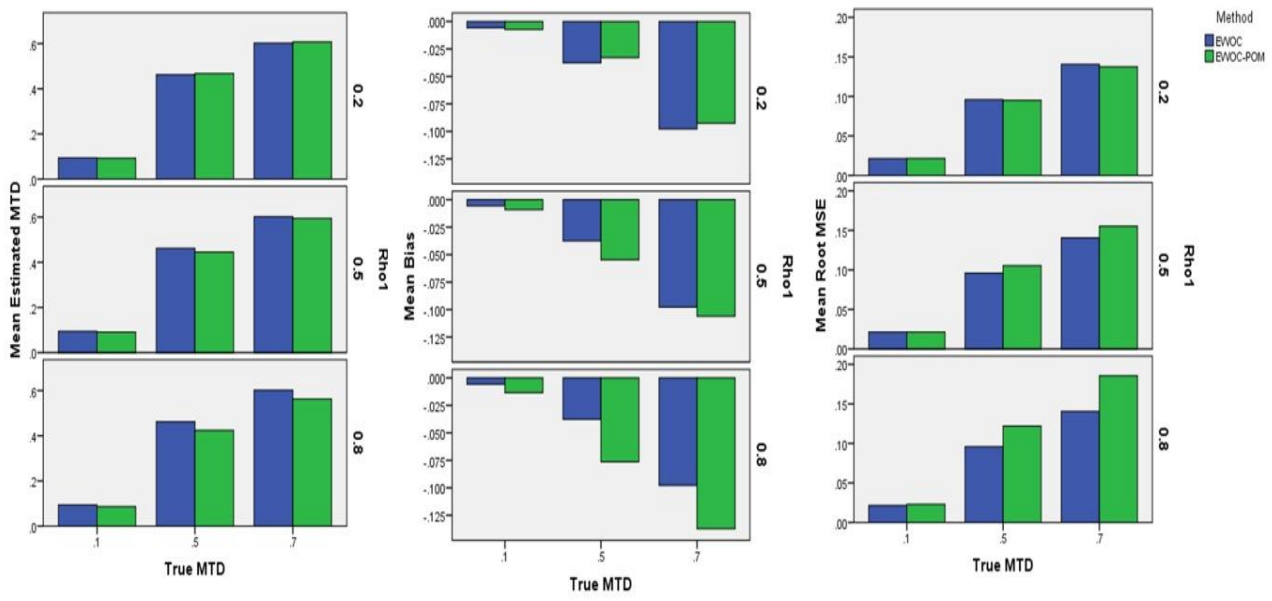

Figure 4. Summary statistics for trial efficiency for EWOC and EWOC-POM under all scenarios. Each graph represents a mean value obtained from all patients from all 1000 trials.

Scenarios	Percent of trial with estimated MTD within 0.05 of γ		Percent of trial with estimated MTD within 0.10 of γ		Percent of Trial with rate of DLT > 0.4	
	EWOC	EWOC-POM	EWOC	EWOC-POM	EWOC	EWOC-POM
$\gamma = 0.1, \rho_1 = 0.2$	98.3	98.4	100	100	7.5	6.6
$\gamma = 0.1, \rho_1 = 0.5$	98.3	97.5	100	100	7.5	3.0
$\gamma = 0.1, \rho_1 = 0.8$	98.3	96.4	100	100	7.5	2.9
$\gamma = 0.5, \rho_1 = 0.2$	39.6	40.5	70.3	71.3	0.2	0.0
$\gamma = 0.5, \rho_1 = 0.5$	39.6	35.6	70.3	63.2	0.2	0.0
$\gamma = 0.5, \rho_1 = 0.8$	39.6	31.0	70.3	59.4	0.2	0.0
$\gamma = 0.7, \rho_1 = 0.2$	24.3	27.6	49.1	53.3	0.0	0.0
$\gamma = 0.7, \rho_1 = 0.5$	24.3	23.2	49.1	45.7	0.0	0.0
$\gamma = 0.7, \rho_1 = 0.8$	24.3	20.1	49.1	37.1	0.0	0.0

Table 1. Percent of trials with estimated MTD within 5% of the dose range and 10% of the dose range of the true MTD γ and percent of trials for which the rate of DLT exceeds 40% for EWOC and EWOC-POM under the nine scenarios.